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(54) Title: RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

(57) Abstract: The present invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with respiratory and pulmonary disease, such as severe acute respiratory syndrome (SARS) virus genes, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful for modulating the expression and activity of SARS virus genes, or other genes involved in pathways of SARS virus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of SARS virus RNA.



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**RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE
RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING
SHORT INTERFERING NUCLEIC ACID (siNA)**

This application claims the benefit of U.S. Provisional Application No. 5 60/462,874, filed April 15, 2003, and is a continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003. This application 10 is also a continuation-in-part of US Patent Application No. 10/427,160, filed April 30, 2003.

Reference is made to International Patent Application No. PCT/US03/05346, filed February 20, 2003, and International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 15 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002, U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 20 filed January 15, 2003. Reference is also made to International Patent Application No. PCT/US02/15876 filed May 17, 2002.

All the listed applications are hereby incorporated by reference herein in their entireties, including the drawings.

Field Of The Invention

25 The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of diseases and conditions that respond to the modulation of severe acute respiratory syndrome (SARS) associated coronavirus (SARS virus) gene expression and/or activity. The present invention also concerns compounds, compositions, and methods relating to conditions and diseases that respond to the 30 modulation of expression and/or activity of genes involved in SARS virus pathways of

gene expression, including cellular genes that are involved in SARS virus infection. Specifically, the invention comprises small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of
5 mediating RNA interference (RNAi) against severe acute respiratory syndrome (SARS) associated coronavirus gene expression.

Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an
10 admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Fire *et al.*, 1998, *Nature*, 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951; Lin *et al.*, 1999, *Nature*, 402, 128-129; Sharp, 1999, *Genes &*
15 *Dev.*, 13:139-141; and Strauss, 1999, *Science*, 286, 886). The corresponding process in plants (Heifetz *et al.*, International PCT Publication No. WO 99/61631) is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression
20 of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or
25 viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from other known mechanisms involving double stranded RNA-specific ribonucleases, such as the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-
30 specific cleavage of mRNA by ribonuclease L (see for example US Patent Nos.

6,107,094; 5,898,031; Clemens *et al.*, 1997, *J. Interferon & Cytokine Res.*, 17, 503-524; Adah *et al.*, 2001, *Curr. Med. Chem.*, 8, 1189).

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer (Bass, 2000, *Cell*, 101, 235; Zamore *et al.*, 2000, *Cell*, 101, 25-33; Hammond *et al.*, 2000, *Nature*, 404, 293). Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2000, *Cell*, 101, 235; Bernstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). Dicer has also been implicated in the excision of 21 and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494 and Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide

overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell*, 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164). In addition, Elbashir *et al.*, *supra*, also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, International PCT Publication No. WO 00/44914, and Beach *et al.*, International PCT Publication No. WO 01/68836 preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.*, Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications would be tolerated in dsRNA molecules.

Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, tested certain chemical modifications targeting the *unc-22* gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that RNAs with two phosphorothioate modified bases also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.

The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes. Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA

molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plaetinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules. Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Pachuck *et al.*, International PCT Publication No. WO 00/63364, describe certain long (at least 200 nucleotide) dsRNA constructs. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050 and 1998, *PNAS*, 95, 13959-13964, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the unc-22 gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al.*, International PCT Publication No. WO 01/53475, describe certain methods for isolating a *Neurospora* silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*,

International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.* International PCT Publications Nos. WO 02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, *Antisense & Nucleic Acid Drug Development*, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, *RNA*, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules.

McCaffrey *et al.*, 2002, *Nature*, 418, 38-39, describes the use of certain siRNA constructs targeting a chimeric SARS NS5B protein/luciferase transcript in mice.

Randall *et al.*, 2003, *PNAS USA*, 100, 235-240, describe certain siRNA constructs targeting SARS RNA in Huh7 hepatoma cell lines.

SUMMARY OF THE INVENTION

This invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with the development or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and/or other disease states associated with SARS virus infection,, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful

for modulating the expression and activity of severe acute respiratory syndrome (SARS) associated coronavirus or genes involved in severe acute respiratory syndrome (SARS) associated coronavirus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of severe acute respiratory syndrome (SARS) associated coronavirus. For convenience, all forms of the small nucleic acid molecules of the invention (*e.g.*, siRNA, dsRNA, micro-RNA, etc.) are referred to herein as "siNA," unless expressly stated otherwise.

A siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating repeat expansion gene expression or activity in cells by RNA interference (RNAi). The use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant invention are useful reagents and are useful in methods for a variety of therapeutic, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus. Specifically, the present invention comprises siNA molecules that modulate the expression of SARS proteins, for example, proteins encoded by SARS virus genome, such as Genbank Accession Nos. in Table I.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of genes representing cellular targets for SARS virus infection, such as cellular receptors,

cell surface molecules, cellular enzymes, cellular transcription factors, and/or cytokines, second messengers, and cellular accessory molecules.

Due to the high sequence variability of the SARS genome, selection of siNA molecules for broad therapeutic applications preferably involve the conserved regions of the SARS genome. In one embodiment, the present invention comprises siNA molecules that target the conserved regions of the SARS genome, such as the polymerase encoding region of the SARS virus genomic RNA. Therefore, siNA molecules of the invention are designed to target all the different isolates of SARS. siNA molecules designed to target conserved regions of various SARS isolates enable efficient inhibition of SARS replication in diverse patient populations and ensure the effectiveness of the siNA molecules against SARS quasi species that evolve due to mutations in the non-conserved regions of the SARS genome. Therefore, a single siNA molecule can be targeted against all isolates of SARS by designing the siNA molecule to interact with conserved nucleotide sequences of SARS (such conserved sequences are expected to be present in the RNA of all SARS isolates).

In one embodiment, a siNA molecule is designed to target the 3'-untranslated region and/or the shared leader sequence of genomic SARS RNA transcripts. Because SARS coronavirus mRNAs are nested with the genomic RNA and share common 3' region and polyA region, a single siNA targeting the 3'-end can target all transcripts plus the genomic RNA.

In one embodiment, a siNA molecule of the invention targets both the plus (genomic) strand RNA and minus strand RNA of the SARS virus. Because the SARS virus generates a minus strand RNA from plus strand genomic RNA, a double stranded siNA molecule targeting the plus strand will also target the minus strand, thus allowing a single double-stranded siNA to target both the plus (genomic) and the minus strand of the SARS virus. For example, a double stranded siNA molecule targeting the 3'-end of the SARS virus genomic strand will also target the 3'-end of the the minus strand, thus allowing a single double-stranded siNA to target both the plus and the minus strand of the SARS virus.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus and/or cellular proteins associated with the maintenance or development of SARS virus infection and/or acute respiratory failure, viral pneumonia, such as genes encoding sequences comprising those sequences referred to by GenBank Accession Nos. shown in Table I, referred to herein generally as SARS. The description below of the various aspects and embodiments of the invention is provided with reference to exemplary severe acute respiratory syndrome (SARS) associated coronavirus genes, generally referred to herein as SARS. However, such reference is meant to be exemplary only and the various aspects and embodiments of the invention are also directed to other genes that express alternate SARS genes, such as mutant SARS genes, splice variants of SARS genes, and genes encoding different strains of SARS, as well as as cellular targets for SARS, such as those described herein. The various aspects and embodiments are also directed to other genes involved in SARS pathways, including genes that encode cellular proteins involved in the maintenance and/or development of SARS virus infection and/or acute respiratory failure or other genes that express other proteins associated with SARS virus infection, such as cellular proteins that are utilized in the SARS life-cycle. Such additional genes can be analyzed for target sites using the methods described herein for SARS. Thus, the inhibition and the effects of such inhibition of the other genes can be performed as described herein. In other words, the term "SARS" as it is defined herein below and recited in the described embodiments, is meant to encompass genes associated with the development or maintenance of SARS virus infection, such as genes which encode SARS polypeptides, including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as cellular genes involved in SARS pathways of gene expression, replication, and/or SARS activity. Also, the term "SARS" as it is defined herein and recited in the described embodiments, is meant to encompass SARS viral gene products and cellular gene products involved in SARS virus infection, such as those described herein. Thus, each of the embodiments described herein with reference to the term "SARS" are applicable to all of the virus, cellular and viral protein, peptide, polypeptide, and/or polynucleotide molecules covered by the term "SARS" as that term is defined herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a severe acute respiratory syndrome virus (e.g., SARS) gene, wherein said siNA molecule comprises about 19 to about 23 base pairs. Preferably the number of based pairs in the siNA molecule is 18, 19, 20, 21, 22, 23, or 24.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS non-coding sequence or regulatory elements involved in SARS gene expression.

In one embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having SARS encoding sequence, such as those sequences having GenBank Accession Nos. shown in Table I. In another embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other SARS encoding sequence, for example other mutant SARS genes not shown in Table I but known in the art to be associated with respiratory and/or pulmonary disease, SARS virus infection and/or acute respiratory failure, viral pneumonia, impeded respiration, respiratory distress syndrome, pulmonary hypertension, or pulmonary vasoconstriction. Chemical modifications as shown in Tables III and IV or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes nucleotide sequence that can interact with nucleotide sequence of a SARS gene and thereby mediate silencing of SARS gene expression, for example, wherein the siNA mediates regulation of SARS gene expression by cellular processes that modulate the chromatin structure of the SARS gene and prevent transcription of the SARS gene.

In another embodiment, the invention features a siNA molecule comprising nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of

a SARS gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a SARS gene sequence or a portion thereof.

In one embodiment, the antisense region of SARS siNA constructs can comprise a sequence complementary to sequence having any of SEQ ID NOs. 1-1651 or 3303-3318. In one embodiment, the antisense region can also comprise sequence having any of SEQ ID NOs. 1652-3302, 3319-3326, 3335-3342, 3351-3358, 3367-3374, 3376, 3378, 3380, 3383, 3385, 3387, 3389, or 3392. In another embodiment, the sense region of the SARS constructs can comprise sequence having any of SEQ ID NOs. 1-1651, 3303-3310, 3311-3318, 3327-3334, 3343-3350, 3359-3366, 3375, 3377, 3379, 3381, 3382, 3384, 3386, 3388, 3390, or 3391.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOs. 1-3392. The sequences shown in SEQ ID NOs: 1-3392 are not limiting. A siNA molecule of the invention can comprise any contiguous SARS sequence (e.g., about 19 to about 25, or about 19, 20, 21, 22, 23, 24 or 25 contiguous SARS nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in Table I. Chemical modifications in Tables III and IV and described herein can be applied to any siNA construct of the invention. siNA molecules of the invention are unmodified or have up to all nucleotides modified with modifications according to Tables III and IV.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense strand is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences with at least about 19 complementary nucleotides.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein said sense region and said antisense region comprise a linear molecule with at least about 19 complementary nucleotides.

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof encoding a SARS protein. The siNA further comprises a sense strand, wherein said sense strand comprises a nucleotide sequence of a SARS gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence encoding a SARS protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a SARS gene or a portion thereof.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a SARS gene. Because SARS genes can share some degree of sequence homology with each other, siNA molecules can be designed to target a class of SARS genes or alternately specific SARS genes by selecting sequences that are either shared among different SARS targets (e.g., different viral strains) or alternatively that are unique for a specific SARS target (e.g., a particular viral strain). Therefore, in one embodiment, the siNA molecule can be designed to target conserved regions of SARS RNA sequences having homology among several SARS genes so as to target several SARS genes (e.g., different SARS isoforms, splice variants, mutant genes etc.) with one siNA molecule. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific SARS RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi activity.

In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplexes containing about 19 base pairs between oligonucleotides comprising about 19 to about 25 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplexes with overhanging ends of about about 1 to about 3 (e.g., 1, 2, 3, or 4) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs.

10 In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for SARS expressing nucleic acid molecules, such as RNA encoding a SARS protein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides, 15 "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al.*, *supra*, 20 applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides 25 can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 30 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA

molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total
5 number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene. In one embodiment, a double stranded siNA molecule comprises one or more chemical
10 modifications and each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule comprises about 19 to about 23 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26,
15 27, 28, or 29) nucleotides, wherein each strand comprises about 19 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the SARS gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence
20 substantially similar to the nucleotide sequence of the SARS gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the SARS gene or a portion
25 thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In one embodiment, the antisense region and the sense region each comprise about 19 to about 23 (e.g. about 19, 20, 21, 22, or 23) nucleotides, wherein the antisense region comprises about 19 nucleotides that are complementary to nucleotides of the sense
30 region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA
5 encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus minus strand RNA. In another embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus plus strand RNA.

10 In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule of the invention comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising Stab00-Stab22 or any combination thereof (see Table IV)) and/or any length described herein can comprise blunt ends or
15 ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e., where a blunt end does not have any overhanging nucleotides. In a non-limiting example, a blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another example,
20 a siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises one blunt end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt
25 ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 18 to about 30 nucleotides (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA
30 molecule can comprise mismatches, bulges, loops, or wobble base pairs, for example, to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are
5 complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the
10 antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein
15 the siNA molecule comprises about 19 to about 21 base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a
20 nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the
25 nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

5 In one embodiment, a siNA molecule of the invention comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 19 to about 23 nucleotides and the antisense region
10 comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS gene, or a
15 portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In another embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the
20 antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, the invention features a double-stranded short interfering
25 nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA
30 molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine

nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides.

- 5 In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In
- 10 another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

- In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein
- 15 the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In another embodiment, the terminal cap moiety is an inverted
- 20 deoxy abasic moiety or glyceryl moiety. In another embodiment, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

- In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. The siNA can be, for example, of length between about 12 and about 36 nucleotides. In
- 25 another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another
- 30 embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-

deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a

nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy- purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of a SARS transcript having sequence unique to a particular SARS disease related allele, such as sequence comprising a SNP associated with the disease specific allele. As such, the antisense region of a siNA molecule of the invention can comprise sequence complementary to sequences that are unique to a particular allele to provide specificity in mediating selective RNAi against the disease related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the

RNA encoded by the SARS gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the SARS gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally includes a phosphate group.

- 5 In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SARS RNA sequence (e.g., wherein said target RNA sequence is encoded by a SARS gene involved in the SARS pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 21 nucleotides long.
- 10 Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in Table IV in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, or Stab 18/20.
- 15 In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a SARS RNA via RNA interference, wherein each strand of said RNA molecule is about 21 to about 23 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the SARS RNA for the RNA molecule to direct cleavage of the
- 20 SARS RNA via RNA interference; and wherein at least one strand of the RNA molecule comprises one or more chemically modified nucleotides described herein, such as deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-O-methoxyethyl nucleotides etc.

In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

25

In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a SARS gene,

wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 18 to about 28 or more (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or more) nucleotides long.

5 In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense
10 strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises
15 nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

20 In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA that encodes a protein or portion thereof, the other strand is a sense strand which comprises
25 nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded
30 siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other

strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 18 to about 29 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein each strand comprises at least about 18 nucleotides that are complementary to the nucleotides of the other strand. In another embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In yet another embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein each of the two strands of the siNA molecule comprises about 21 nucleotides. In one embodiment, about 21 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In another embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof. In another embodiment, about 21 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the SARS RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the SARS RNA or a portion thereof that is present in the SARS RNA.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of

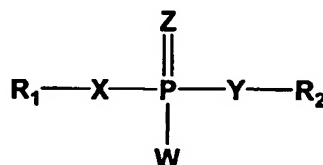
a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native
5 unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments
10 of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or
15 backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a
20 nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise
25 sequence complementary to a RNA or DNA sequence encoding SARS and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.

In one embodiment, the nucleotide sequence of the antisense strand or a portion thereof of a siNA molecule of the invention is complementary to the nucleotide sequence of a SARS RNA or a portion thereof that is present in the RNA of all SARS isolates.

In one embodiment, the invention features a chemically-modified short interfering
 5 nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:

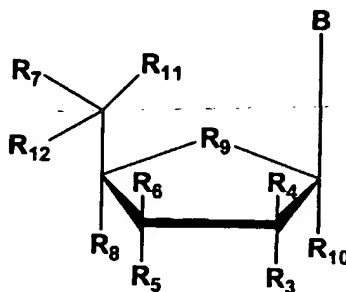


10 wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of
 15 the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, Nucleic Acids Research, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense
 20 strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more
 25 (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine

nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:

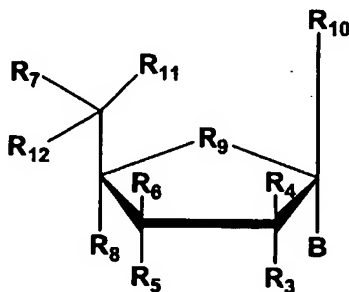


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine,

pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:



20

wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-

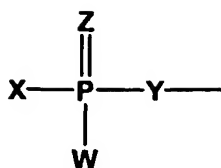
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aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R₉ is O, S, CH₂, S=O, CHF, or CF₂, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

- 5 In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a strand complementary to a target RNA, wherein the siNA molecule comprises an all RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand wherein the siNA molecule also comprises about 1 to about 3 (e.g., about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (e.g., about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA molecule having chemical modifications having any of Formulae I-VII.

- In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and

5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) 2'-deoxy,

2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more

phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5' internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36 to about 70 (*e.g.*, about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31,

32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to about 23 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 20 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is

biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising
5 sense and antisense regions, wherein the antisense region is about 16 to about 25 (*e.g.*, about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region is about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more
10 chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 22 (*e.g.*, about 18, 19, 20, 21, or 22) nucleotides in length and
15 wherein the sense region is about 3 to about 15 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetric double stranded siNA
20 molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

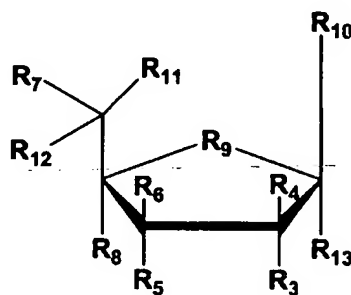
In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (*e.g.*, about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18,
25 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a
30 chemical modification having any of Formulae I-VII or any combination thereof,

wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable.

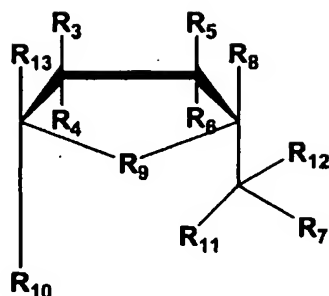
- 5 For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

- 10 In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



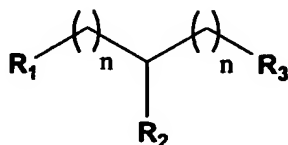
- wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.

- 20 In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R₃, R₄, R₅, R₆, R₇, R₈, R₁₀, R₁₁, R₁₂, and R₁₃ is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R₉ is O, S, CH₂, S=O, CHF, or CF₂, and either R₂, R₃, R₈ or R₁₃ serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each n is independently an integer from 1 to 12, each R₁, R₂ and R₃ is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or a group having Formula I, and R₁, R₂ or R₃ serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups, $n = 1$, and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in Figure 10).

In another embodiment, a moiety having any of Formula V, VI or VII of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, a moiety having Formula V, VI or VII can be present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-

2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine

nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or

more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein
5 any (e.g., one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or
10 more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention capable of mediating RNA interference
15 (RNAi) against SARS inside a cell or reconstituted *in vitro* system comprising a sense region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine
20 nucleotides present in the sense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro
25 pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). The sense region and/or the antisense region can have a
30 terminal cap modification, such as any modification described herein or shown in Figure 10, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the

sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in Figures 4 and 5 and Tables III and IV herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Also, in any of these embodiments, one or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Additionally, in any of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring

ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2'-O, 4'-C-methylene-(D-ribofuranosyl) nucleotides); 2'-methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example Figure 10) such as an inverted deoxyabaisc moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any

combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human
5 serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, filed July 22, 2002, incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention
10 can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for
15 example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the
20 invention can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule
25 in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those
30 in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin.*

Mol. Ther., 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, 18:6353 and *Nucleic Acids Res.* 1987, 15:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, 113:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, 113:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, 21:2585 and *Biochemistry* 1993, 32:1751; Durand *et al.*, *Nucleic Acids Res.* 1990, 18:6353; McCurdy *et al.*, *Nucleosides & Nucleotides* 1991, 10:287; Jsckke *et al.*, *Tetrahedron Lett.* 1993, 34:301; Ono *et al.*, *Biochemistry* 1991, 30:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, 113:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted *in vitro* system, wherein one or both strands of the siNA molecule that are assembled from two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA comprise separate oligonucleotides not having any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as described herein, wherein the oligonucleotide does not have any

ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presense of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within the siNA can
5 include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA
10 molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a
15 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the single stranded siNA molecule of the invention comprises about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all
20 the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA
25 molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are
30 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine

nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in Figure 10, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA
5 optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal
10 phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense
15 and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or
20 alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation
25 (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, the invention features a method for modulating the expression
30 of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the

siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

10 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

15 In another embodiment, the invention features a method for modulating the expression of two or more SARS genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the SARS genes and wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

20 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA

molecule into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

5 In one embodiment, siNA molecules of the invention are used as reagents in *ex vivo* applications. For example, siNA reagents are introduced into tissue or cells that are transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in vivo. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeting a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

25 In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate

the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

5 In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular
10 organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS genes in that organism.

15 In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of
20 the SARS gene in the organism. The level of SARS protein or RNA can be determined as is known in the art.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the
25 siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism. The level of SARS protein or RNA can be determined as is known in the art.

In one embodiment, the invention features a method for modulating the expression
30 of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the

invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) contacting the cell in vitro or in vivo with the siNA molecule under
10 conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b)
15 contacting the cell of the tissue explant derived from a particular organism with the siNA molecule under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that
20 organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS
25 gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS
30 genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising contacting the organism with a siNA molecule of the invention under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising contacting the organism with one or more siNA molecules of the invention under conditions suitable to modulate the expression of the SARS genes in the organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (e.g., SARS) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish among the functions of gene family members. For example, a protein that contains an

alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as SARS family genes. As such, siNA molecules targeting multiple SARS targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example SARS genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in Table I.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of

a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described
5 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the
10 art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of 4^N , where N represents the number of base paired nucleotides in each of the siNA construct
15 strands (eg. for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be 4^{19}); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target SARS RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the
20 siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 7 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of SARS RNA are
25 analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target SARS RNA sequence. The target SARS RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

30 In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets

of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. Fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for

treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a method for reducing or preventing tissue rejection in a subject comprising administering to the subject a composition of the invention under conditions suitable for the reduction or prevention of tissue rejection in the subject.

In another embodiment, the invention features a method for validating a SARS gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a cell, tissue, or organism under conditions suitable for modulating expression of the SARS target gene in the cell, tissue, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, or organism.

In another embodiment, the invention features a method for validating a SARS target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the SARS target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi activity. The term "biological system" includes, for example, a cell, tissue, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size, proliferation, motility, protein expression or RNA expression or other physical or

chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Florescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

5 In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of a SARS target gene in a biological system, including, for example, in a cell, tissue, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that
10 can be used to modulate the expression of more than one SARS target gene in a biological system, including, for example, in a cell, tissue, or organism.

In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another
15 embodiment, the cell containing a siNA molecule of the invention is a human cell.

In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions
20 suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of
25 the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety
30 than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under

conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are synthesized in tandem using a cleavable linker attached to the first sequence which acts a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide

sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to
5 hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled
10 pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place
15 either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an
20 oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the
25 deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the
30 invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against SARS in a cell, wherein the chemical modifications do not

significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

5 In another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

10 In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

15 In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

20 In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

25 In another embodiment, the invention features a method for generating siNA molecules against SARS with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct,

for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394
5 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability, comprising (a) introducing a conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved
10 bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or
15 spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically
20 modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary
25 to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or
30 improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in Figure 10, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in Figure 10, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting

the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In

5 another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in Figure 10 (e.g. inverted deoxyabasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating

10 RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude

15 recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for example, can result in a molecule where the 5'-end of the sense strand no longer has a

20 free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

25 In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule

30 from acting as a template or guide sequence for RNAi activity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have

complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and (c) introducing chemical modifications (e.g. chemical modifications as described herein or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be present on the surface of a cell or can alternately be an intercellular receptor. Interaction

of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

5 In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

10 In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

15 In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 2,000 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al*, US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman *et al.*, USSN 60/402,996).
25 Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene

expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.*, 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.*, 2002, *RNA*, 8, 842-850; Reinhart *et al.*, 2002, *Gene & Dev.*, 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in Figures 4-6, and Tables II and III herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 19 base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having

self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The

5 siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a

10 portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the

15 siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiments, the siNA molecule of the invention comprises

20 separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise

25 nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-

30 nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of

nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however

5 have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON."

10 As used herein, the term siNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified

15 siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the

20 pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure to alter gene expression (see, for example, Verdel *et al.*, 2004, *Science*, 303, 672-676; Pal-Bhadra *et al.*, 2004, *Science*, 303, 669-672; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837;

25 Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example Figures 14-15 and Vaish *et al.*, USSN 10/727,780 filed December 3, 2003).

30 In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example Figures 16-22 and Jadhav *et al.*, USSN 60/543,480, filed February 10,

2004). The multifunctional siNA of the invention can comprise sequence targeting, for example, two regions of SARS RNA (see for example target sequences in Tables II and III) or alternately, SARS RNA and cellular RNA involved in SARS virus infection or replication. In another embodiment, a multifunctional siNA of the invention can
5 comprise sequence targeting for example both viral genes encoding RNAi inhibitory factors and viral genes encoding viral structural proteins.

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense
10 region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g., about 19, 20, 21, or 22) nucleotides) and a loop region comprising about 4 to about 8
15 (e.g., about 4, 5, 6, 7, or 8) nucleotides, and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non-
20 nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and
25 form a duplex. For example, an asymmetric duplex siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g. about 19, 20, 21, or 22) nucleotides) and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region.

30 By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or

activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

5 By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA
10 molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule
15 of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "gene", or "target gene", is meant, a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-
20 coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional
25 or regulatory cellular processes. Abberant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of an organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination,
30 methylation etc.). The target gene can be a gene derived from a cell, an endogenous gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus,

which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include
5 vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts.

By "SARS" or "SARS virus" as used herein is meant the SARS virus or any protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome. The term "SARS" also includes nucleic acid molecules encoding RNA or protein(s) associated with the development and/or maintenance of SARS virus infection,
10 such as nucleic acid molecules which encode SARS RNA or polypeptides (such as polynucleotides having Genbank Accession numbers shown in Table I), including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as genes involved in SARS pathways of gene expression and/or SARS activity. Also, the term "SARS" is meant to encompass SARS viral gene products
15 and genes that modulate cellular targets for SARS virus infection, such as those described herein.

By "SARS protein" or "SARS virus protein" is meant, protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome or alternately, cellular proteins involved in SARS virus infection and/or replication.

By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different
20 members of a gene family, different protein epitopes, different protein isoforms or completely divergent genes, such as a cytokine and its corresponding receptors. A
25 homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence.
30 Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%,

95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one biological system or organism to another biological system or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By "sense region" is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By "antisense region" is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

By "target nucleic acid" is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci. USA* 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides out of a total of 10 nucleotides in the first oligonucleotide being based paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and

100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

5 The siNA molecules of the invention represent a novel therapeutic approach to treat various diseases and conditions, including SARS virus infection, acute respiratory failure, viral pneumonia, and any other indications that can respond to the level of SARS in a cell or tissue. The reduction of SARS expression and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

10 In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently about 18 to about 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (*e.g.*, about 17, 18, 19, 20, 21, 22 or 23). In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to
15 about 55 (*e.g.*, about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44 (*e.g.*, 38, 39, 40, 41, 42, 43 or 44) nucleotides in length and comprising about 16 to about 22 (*e.g.*, about 16, 17, 18, 19, 20, 21 or 22) base pairs. Exemplary siNA molecules of the invention are shown in Table II. Exemplary synthetic siNA molecules of the invention are shown in Table III and/or Figures 4-5.

20 As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, *e.g.*, specifically does not refer to a human. The cell can be present in an organism, *e.g.*, birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (*e.g.*, bacterial cell) or eukaryotic (*e.g.*, mammalian or plant cell). The cell can be of somatic or germ line
25 origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.

The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to
30 relevant tissues *ex vivo*, or *in vivo* through injection, infusion pump or stent, with or

without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in **Tables II-III** and/or **Figures 4-5**. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in **Table IV** can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a β -D-ribo-furanose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term "thiophosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and
5 W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl
10 and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or
15 C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein (e.g., cancers and othe proliferative conditions). For example, to treat a particular disease or condition, the siNA molecules can be administered to a subject or can be
20 administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic
25 agents to treat a disease or condition. Non-limiting examples of other therapeutic agents that can be readily combined with a siNA molecule of the invention are enzymatic nucleic acid molecules, allosteric nucleic acid molecules, antisense, decoy, or aptamer nucleic acid molecules, antibodies such as monoclonal antibodies, small molecules, and other organic and/or inorganic compounds including metals, salts and ions.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector
5 can also contain sequence(s) encoding a single nucleic acid molecule that is self-complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online
10 publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by
15 a Genbank Accession numbers, for example Genbank Accession Nos. shown in Table I.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target
20 RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as
25 described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by
30 administration to target cells ex-planted from a subject followed by reintroduction into

the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

- 5 Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group, remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl on purification method wherein only duplexes/oligonucleotides with the terminal protecting group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in

turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all

pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified
5 internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

Figure 4C: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and
10 wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-
15 terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N)-nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a
20 phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4D: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified
25 nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the
30 target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are

2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown
5 as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4E: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,
10 deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are
15 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4F: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and
20 wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro
25 modified nucleotides and all purine nucleotides that may be present are 2'-deoxy
30 nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,

deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of
5 constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glyceryl moiety (L) is present at the 3'-end of the antisense strand for any construct shown in Figure 4 A-F, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA
10 sequences of the invention. A-F applies the chemical modifications described in Figure 4A-F to a SARS virus siNA sequence. Such chemical modifications can be applied to any SARS sequence and/or SARS polymorphism sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base
15 pairs; however, different embodiments of the invention include any number of base pairs described herein. Bracketed regions represent nucleotide overhangs, for example comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as
20 a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the
25 active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

Figure 7A: A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

Figure 7B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a SARS target sequence and having self-complementary sense and antisense regions.

Figure 7C: The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology*, 29, 505-508.

Figure 8A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

Figure 8A: A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

Figure 8B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence.

Figure 8C: The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense

strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

Figure 9B&C: (Figure 9B) The sequences are pooled and are inserted into vectors such that (Figure 9C) transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

Figure 9E: The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including (1) [3'-3']-inverted deoxyribose; (2) deoxyribonucleotide; (3) [5'-3']-3'-deoxyribonucleotide; (4) [5'-3']-ribonucleotide; (5) [5'-3']-3'-O-methyl ribonucleotide; (6) 3'-glyceryl; (7) [3'-5']-3'-deoxyribonucleotide; (8) [3'-3']-deoxyribonucleotide; (9) [5'-2']-deoxyribonucleotide; and (10) [5'-3']-dideoxyribonucleotide. In addition to modified and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

Figure 11 shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-mofications, base modifications, backbone modifications, terminal cap modifications etc). The modified construct is tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

Figure 12 shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

Figure 13 shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

Figure 14A shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are identified in a target nucleic acid sequence. (i) A palindrome or repeat sequence is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palindrome sequence. (iii) An inverse repeat sequence of the non-palindrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO molecule comprising sequence complementary to the nucleic acid target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. **Figure 14B** shows a non-limiting representative example of a duplex forming oligonucleotide sequence. **Figure 14C** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. **Figure 14D** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

Figure 15 shows a non-limiting example of the design of self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palindrome/repeat sequences allow the design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palindrome (shown as XYXYXY in the Figure). An inverse repeat of the non-palindrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

Figure 16 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. Figure 16A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. Figure 16B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 17A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 17B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 16**.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 18A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and

wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 18B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 19A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 19B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a

second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in Figure 18.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent biologic pathway that is implicated in the maintenance of progression of disease. Each strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid sequences within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target region. These

design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Mechanism of Action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or "improved RNAi activity" is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*, 1998, *Nature*, 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999,

Trends Genet., 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Bernstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from Dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes.

Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably through cellular mechanisms that regulate chromatin structure and thereby prevent transcription of target gene sequences (see for example Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237). As such, siRNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA.

5 Elbashir *et al.*, 2001, *Nature*, 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown

10 that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi

15 activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA

20 (Nykanen *et al.*, 2001, *Cell*, 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using

25 automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous

30 delivery. The simple structure of these molecules increases the ability of the nucleic acid

to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (e.g., certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μ mol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μ mol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μ L of 0.11 M = 6.6 μ mol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μ L of 0.25 M = 15 μ mol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μ L of 0.11 M = 4.4 μ mol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μ L of 0.25 M = 10 μ mol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained

from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the
5 polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants,
10 containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and
15 makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 µmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides.
20 Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 µmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 µL of 0.11 M = 6.6 µmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 µL of 0.25 M = 15
25 µmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 µL of 0.11 M = 13.2 µmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 µL of 0.25 M = 30 µmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc.
30 synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems,

- Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.).
- 5 Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide) 0.05 M in acetonitrile) is used.
- 10 Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of
- 15 EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 µL of a solution of 1.5 mL *N*-methylpyrrolidinone, 750 µL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C.
- 20 After 1.5 h, the oligomer is quenched with 1.5 M NH₄HCO₃.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is

25 heated at 65 °C for 15 minutes. The sample is cooled at -20 °C and then quenched with 1.5 M NH₄HCO₃.

For purification of the trityl-on oligomers, the quenched NH₄HCO₃ solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is

30 detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with

water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No. WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection.

The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are synthesized as a single contiguous oligonucleotide fragment or strand-separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can

be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al.*, *supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

5 In another aspect of the invention, siNA molecules of the invention are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that
10 provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) can prevent their degradation by serum ribonucleases, which can increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO
15 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.*, U.S. Pat. No. 6,300,074; and Burgin *et al.*, *supra*; all of which are incorporated by reference herein). All of the
20 above references describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules described herein. Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired.

25 There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-O-
30 allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992, -

TIBS. 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al.*, *International Publication* PCT No. WO 92/07065; Perrault *et al.* *Nature*, 1990, 344, 565-568; Pieken *et al.* *Science*, 1991, 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman *et al.* *International Publication* PCT No. WO 93/15187; Sproat, U.S. Pat. No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, *International PCT publication* No. WO 97/26270; Beigelman *et al.*, U.S. Pat. No. 5,716,824; Usman *et al.*, U.S. Pat. No. 5,627,053; Woolf *et al.*, *International PCT Publication* No. WO 98/13526; Thompson *et al.*, USSN 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the

goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic

acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers.

5 These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker
10 molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the
15 invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino,
20 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or
25 phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or
30 molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in

combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

10 The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

Therapeutic nucleic acid molecules (e.g., siNA molecules) delivered exogenously
15 optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify
20 nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.
25

Use of the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with
30 combinations of molecules, including different motifs and/or other chemical or

biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

- 5 In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'-cap structure, for example on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.*, U.S. Pat. No. 10 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide, 4'-thio nucleotide; 15 carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic moiety; 20 moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, 25 inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; 30 phosphorodithioate; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide

moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 5 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not 10 contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 15 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. 20 More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂, halogen, N(CH₃)₂, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, 25 including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*, all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (e.g., 5-methylcytidine), 5-alkyluridines (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090;

Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate, carbamate, carboxymethyl, acetamidate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of β -D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH₂ or 2'-O- NH₂, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.*, U.S. Pat. No. 6,248,878, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, *e.g.*, to

enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Administration of Nucleic Acid Molecules

A siRNA molecule of the invention can be adapted for use to treat for example
5 SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue, alone or in combination with other therapies. For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the
10 delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.*, 1999, *Mol. Membr. Biol.*, 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.*, 137, 165-192; and Lee *et al.*, 2000, *ACS Symp. Ser.*, 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.*, U.S. Pat. No.
15 6,395,713 and Sullivan *et al.*, PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles,
20 such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang *et al.*, International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLGA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and
25 bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.
30

Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump.

In one embodiment, the nucleic acid molecules or the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation administered by an inhalation device or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. Solid particulate compositions containing respirable dry particles of micronized nucleic acid compositions can be prepared by grinding dried or lyophilized nucleic acid compositions, and then passing the micronized composition through, for example, a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the nucleic acid compositions of the invention can optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which can be blended with the nucleic acid compound in any suitable ratio, such as a 1 to 1 ratio by weight.

Aerosols of liquid particles comprising a nucleic acid composition of the invention can be produced by any suitable means, such as with a nebulizer (see for example US 4,501,729). Nebulizers are commercially available devices which transform solutions or suspensions of an active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride or other suitable salts. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, anti-oxidants, flavorings, volatile oils, buffering agents and emulsifiers and other formulation surfactants. The aerosols of solid particles comprising the active composition and surfactant can likewise be produced with any solid particulate aerosol generator. Aerosol generators for administering solid particulate therapeutics to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a therapeutic composition at a rate

suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which can be delivered by means of an insufflator. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the

5 treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as

10 lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted

15 to deliver a metered volume to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, emulsifiers and other formulation surfactants, such as oleic acid or

20 sorbitan trioleate, anti-oxidants and suitable flavoring agents. Other methods for pulmonary delivery are described in, for example US Patent Application No. 20040037780, and US Patent Nos. 6,592,904; 6,582,728; 6,565,885.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Application

25 Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

30 Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and

the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable administration, and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the

association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells producing excess repeat expansion genes.

- 5 By "pharmaceutically acceptable formulation" is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85);
- 10 biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery (Emerich, DF *et al.*, 1999, *Cell Transplant*, 8, 47-58); and loaded nanoparticles, such as those made of polybutylcyanoacrylate. Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596;
- 15 Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

- The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-
- 20 circulating liposomes or stealth liposomes). These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al.* *Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al.*, *Chem.*
- 25 *Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al.*, *Science* 1995, 267, 1275-1276; Oku *et al.*, 1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to
- 30 conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al.*, *J. Biol. Chem.* 1995, 270, 24864-24870; Choi *et al.*, International PCT

Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid
5 accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described,
10 for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

15 A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence; or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent
20 medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage
25 unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a
30 pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically

acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard
5 or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable
10 preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for
15 example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl
20 monostearate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

25 Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example,
30 lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain

aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a

demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above.

5 The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any

10 bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at

15 ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either

20 be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be

25 combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age,

30 body weight, general health, sex, diet, time of administration, route of administration,

and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example, triantennary structures are bound with greater affinity than biantennary or monoantennary chains (Baenziger and Fiete, 1980, *Cell*, 22, 611-620; Connolly *et al.*, 1982, *J. Biol. Chem.*, 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect" has also been described for the binding and uptake of mannosyl-terminating glycoproteins or glycoconjugates (Ponpipom *et al.*, 1981, *J. Med. Chem.*, 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavailability,

pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.*, USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.*, USSN 10/151,116, filed May 17, 2002. In one embodiment, 5 nucleic acid molecules of the invention are complexed with or covalently attached to nanoparticles, such as Hepatitis B virus S, M, or L envelope proteins (see for example Yamado *et al.*, 2003, *Nature Biotechnology*, 21, 885). In one embodiment, nucleic acid molecules of the invention are delivered with specificity for human tumor cells, specifically non-apoptotic human tumor cells including for example T-cells, hepatocytes, 10 breast carcinoma cells, ovarian carcinoma cells, melanoma cells, intestinal epithelial cells, prostate cells, testicular cells, non-small cell lung cancers, small cell lung cancers, etc.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (e.g., Izant and Weintraub, 1985, *Science*, 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.*, 15 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science*, 247, 20 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 25 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) 30 inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited

to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); and c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention, wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisiewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells (Thompson *et al.*, *supra*; Couture and Stinchcomb, 1996, *supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, *supra*).

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule,

wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

SARS virus biology and biochemistry

The following discussion is adapted from the report, "Preliminary Clinical Description of Severe Acute Respiratory Syndrome", World Health Organization, Geneva, Switzerland, available at the Centers for Disease Control and Prevention website.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS

global outbreak of 2003 was contained. According to the World Health Organization (WHO), a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak. Of these, 774 died.

5 The incubation period for SARS is typically 2--7 days; however, isolated reports have suggested an incubation period as long as 10 days. The illness begins generally with a prodrome of fever ($>100.4^{\circ}\text{F}$ [$>38.0^{\circ}\text{C}$]). Fever often is high, sometimes is associated with chills and rigors, and might be accompanied by other symptoms, including headache, malaise, and myalgia. At the onset of illness, some persons have mild respiratory symptoms. Typically, rash and neurologic or gastrointestinal findings are
10 absent; however, some patients have reported diarrhea during the febrile prodrome.

After 3--7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea, which might be accompanied by or progress to hypoxemia. In 10%--20% of cases, the respiratory illness is severe enough to require intubation and mechanical ventilation. Death may result from progressive respiratory
15 failure due to alveolar damage. The case-fatality rate among persons with illness meeting the current WHO case definition of SARS is approximately 3%.

Chest radiographs might be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal interstitial infiltrates progressing to more generalized,
20 patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS also have shown areas of consolidation.

Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts have generally been normal or decreased. At the peak of the respiratory illness, approximately 50% of patients have leukopenia and
25 thrombocytopenia or low-normal platelet counts ($50,000\text{--}150,000/\mu\text{L}$). Early in the respiratory phase, elevated creatine phosphokinase levels (as high as $3,000\text{ IU/L}$) and hepatic transaminases (two to six times the upper limits of normal) have been noted. In the majority of patients, renal function has remained normal.

The severity of illness might be highly variable, ranging from mild illness to death. Although a few close contacts of patients with SARS have developed a similar illness, the majority have remained well. Some close contacts have reported a mild, febrile illness without respiratory signs or symptoms, suggesting the illness might not always progress to the respiratory phase.

Treatment regimens have included several antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy also has included antiviral agents such as oseltamivir or ribavirin. Steroids have also been administered orally or intravenously to patients in combination with ribavirin and other antimicrobials. At present, the most efficacious treatment regimen, if any, is unknown.

The causative agent of SARS appears to be a novel coronavirus that was isolated from patients who met the case definition of SARS (see Ksiazek et al., 2003, New England Journal of Medicine, 10.1056/NEJMoa030781. Indirect fluorescent antibody tests and enzyme-linked immunosorbent assays made with the new coronavirus isolate have been used to demonstrate a virus-specific serologic response. Amplification of short regions of the polymerase gene, (the most strongly conserved part of the Coronavirus genome) by reverse transcriptase polymerase chain reaction (RT-PCR) and nucleotide sequencing revealed that the SARS virus is a novel Coronavirus which has not previously been present in human populations. This conclusion is confirmed by serological (antigenic) investigations. The sequence of the SARS associated coronavirus was recently made available through the CDC.

Viral entry into cells occurs via endocytosis and membrane fusion. Replication occurs in the cytoplasm. Initially, the 5' 20kb of the (+)sense genome is translated to produce a viral polymerase, which then produces a full-length (-)sense strand. This is used as a template to produce mRNA as a nested set of transcripts, all with an identical 5' non-translated leader sequence of 72nt and coincident 3' polyadenylated ends. Each mRNA is monocistronic, the genes at the 5' end being translated from the longest mRNA. These unusual cytoplasmic structures are produced not by splicing but by the polymerase during transcription. Between each of the genes there is a repeated intergenic sequence - UCUAAC - which interacts with the transcriptase plus cellular factors to splice the leader sequence onto the start of each ORF. Viral assembly occurs by budding

into the golgi apparatus, and viral particles are transported to the surface of the cell and are subsequently released.

The SARS virus can be grown in Vero cells (a fibroblast cell line isolated in 1962 from a primate). This is a novel property for human coronaviruses which usually cannot be cultivated. In these cells, virus infection results in a cytopathic effect, and budding of Coronavirus-like particles from the endoplasmic reticulum within infected cells.

Detection of the SARS virus can be accomplished with serological testing and molecular diagnostic procedures. Serological testing for anti-Coronavirus antibodies consists of indirect fluorescent antibody testing and enzyme-linked immunosorbent assays (ELISA) which detect antibodies against the virus produced in response to infection. Molecular testing consists of reverse transcriptase-polymerase chain reaction (RT-PCR) tests specific for the RNA from the novel Coronavirus.

The use of small interfering nucleic acid molecules targeting SARS genes therefore provides a class of novel therapeutic agents that can be used in the treatment and diagnosis of SARS virus infection, acute respiratory failure, viral pneumonia, or any other disease or condition that responds to modulation of SARS genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

20 Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-O-DMT) group remains intact (trityl on synthesis), the

oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.

Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see Figure 1) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such as Bromotripyrrolidinophosphoniumhexafluorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M $\text{NH}_4\text{H}_2\text{CO}_3$.

Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV H_2O , and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV H_2O or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The column is then washed, for example with 1 CV H_2O followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with H_2O followed by 1 CV 1M NaCl and additional H_2O . The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA construct only shows a single peak. Testing of the purified siNA construct using a luciferase reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

10 Example 2: Identification of potential siNA target sites in any RNA sequence

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be used. High throughput screening assays can be developed for screening siNA molecules

using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

The following non-limiting steps can be used to carry out the selection of siNAs targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial sequence analysis programs such as Oligo, MacVector, or the GCG Wisconsin Package can be employed as well.
2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can identify subsequences that are unique to a target sequence, such as a mutant target sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.
3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.
5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.
6. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.
7. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.
8. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see Tables II and III). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.
9. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see for example Reynolds *et al.*, 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Ui-Tei *et al.*, 2004, *Nucleic Acids Research*, 32, doi:10.1093/nar/gkh247.

5 In an alternate approach, a pool of siNA constructs specific to a SARS target sequence is used to screen for target sites in cells expressing SARS RNA, such as VERO cells and/or FRhk-4 cells. The general strategy used in this approach is shown in Figure 9. A non-limiting example of such is a pool comprising sequences having SEQ ID NOs: 1-3392. Cells expressing SARS (e.g., VERO cells and/or FRhk-4 cells) are transfected
10 with the pool of siNA constructs and cells that demonstrate a phenotype associated with SARS inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example Figure 7 and Figure 8). The siNA from cells demonstrating a positive phenotypic change (e.g., decreased proliferation, decreased SARS mRNA levels or decreased SARS protein
15 expression), are sequenced to determine the most suitable target site(s) within the target SARS RNA sequence.

Example 4: SARS targeted siNA design

siNA target sites were chosen by analyzing sequences of the SARS RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given
20 sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of
25 the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example
30 those RNA sequences corresponding to the any gene transcript.

Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration in vivo and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantify RNAi activity. Synthetic siNA constructs that possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example Figure 11).

Example 5: Chemical Synthesis and Purification of siNA

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can be synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.*, US Patent Nos. 6,111,086; 6,008,400; 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphosphoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine,

N4 acetyl cytidine, and N2-isobutryl guanosine). Alternately, 2'-O-Silyl Ethers can be used in conjunction with acid-labile 2'-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra*. Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl protection as described by Usman *et al.*, US Patent 5,631,360, incorporated by reference herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3'- to 5'- direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3'-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5'-end of the first nucleoside. The support is then washed and any unreacted 5'-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5'-acetyl moieties. The trivalent phosphorus linkage is then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition cycle, the 5'-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, for example by using differing coupling times, differing reagent/phosphoramidite concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Deprotection and purification of the siNA can be performed as is generally described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra*, incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-

2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

Example 6: RNAi *in vitro* assay to assess siNA activity

- 5 An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting SARS RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with SARS target RNA. A *Drosophila* extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target
- 10 RNA is generated via *in vitro* transcription from an appropriate SARS expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C, then diluted in
- 15 lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide. The *Drosophila* lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the
- 20 supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug/ml creatine phosphokinase, 100 uM GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid.
- 25 The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in
- 30 which siNA is omitted from the reaction.

Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [α - 32 P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'- 32 P-end labeled using T4 polynucleotide kinase enzyme.

- 5 Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by PHOSPHOR IMAGER[®] (autoradiography) quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.

- 10 In one embodiment, this assay is used to determine target sites the SARS RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the SARS RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.

15 Example 7: Nucleic acid-inhibition of SARS target RNA *in vitro*

siNA molecules targeted to the human SARS RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target sequences and the nucleotide location within the SARS RNA are given in **Table II and III**.

- 20 Two formats are used to test the efficacy of siNAs targeting SARS. First, the reagents are tested in cell culture using, for example, VERO cells and/or FRhk-4 cells, to determine the extent of RNA and protein inhibition. siNA reagents (*e.g.*; see **Tables II and III**) are selected against the SARS target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example,
- 25 VERO cells and/or FRhk-4 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (*eg.*, ABI 7700 TAQMAN[®]). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen
- 30 for the target and optimization performed. After an optimal transfection agent

concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

Delivery of siNA to Cells

- 5 Cells (e.g., VERO cells and/or FRhk-4 cells infected with the SARS virus) are seeded, for example, at 1×10^5 cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration 2 μ g/ml) are complexed in EGM basal media (Bio Whittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the
- 10 complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at 1×10^3 in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at
- 15 room temperature. Uptake of siNA is visualized using a fluorescent microscope.

TAQMAN® (real-time PCR monitoring of amplification) and Lightcycler quantification of mRNA

- Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For
- 20 TAQMAN® analysis (real-time PCR monitoring of amplification), dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50 μ l reactions consisting of 10 μ l total RNA, 100 nM forward primer, 900 nM reverse primer,
- 25 100 nM probe, 1X TAQMAN® PCR reaction buffer (PE-Applied Biosystems), 5.5 mM $MgCl_2$, 300 μ M each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AMPLITAQ GOLD® (DNA polymerase) (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C, 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C
- 30 and 1 minute at 60°C. Quantitation of mRNA levels is determined relative to standards

generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/rxn) and normalizing to β -actin or GAPDH mRNA in parallel TAQMAN® reactions (real-time PCR monitoring of amplification). For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcycler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research*, 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hour at 4°C. Following washes, the secondary antibody is applied, for example (1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

Example 8: RNAi mediated inhibition of SARS RNA expression

siNA constructs (e.g., siNA constructs shown in Table III) are tested for efficacy in reducing SARS RNA expression in, for example, VERO cells and/or FRhk-4 cells. Cells are plated approximately 24h before transfection in 96-well plates at 5,000-7,500 cells/well, 100 μ l/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 μ l/well and incubated for 20 minutes at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150 μ l. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the

continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

In a non-limiting example, a siNA construct comprising ribonucleotides and 3'-terminal dithymidine caps is assayed along with a chemically modified siNA construct comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides and purine ribonucleotides in which the sense strand of the siNA is further modified with 5' and 3'-terminal inverted deoxyabasic caps and the antisense strand comprises a 3'-terminal phosphorothioate internucleotide linkage. Additional stabilization chemistries as described in Table IV are similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

Example 9: Animal Models

Evaluating the efficacy of anti-SARS agents in animal models is an important prerequisite to human clinical trials. Byron *et al.*, 2003, *Nature*, 425, 915, describe ferret and feline animal models of SARS virus infection. Haagmans *et al.*, 2004, *Nature Medicine*, 10, 290-293, describe the use of pegylated interferon-alpha in protecting type 1 pneumocytes against SARS coronavirus infection in macaques. Gao *et al.*, 2003, *Lancet*, 362, 1895-6, describe the use of a SARS virus vaccine in monkeys. All of these models can be adapted for use for pre-clinical evaluation of the efficacy of nucleic acid compositions of the invention in modulating SARS virus gene expression toward therapeutic use.

Example 10: Indications

The present body of knowledge in SARS research indicates the need for methods to assay SARS activity and for compounds that can regulate SARS expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of SARS levels. In addition, the nucleic acid molecules can be used to treat disease state related to SARS levels.

Particular degenerative and disease states that can be associated with SARS expression modulation include, but are not limited to, SARS virus infection, liver failure, hepatocellular carcinoma, cirrhosis, and/or other disease states associated with SARS virus infection.

Immunomodulators, steroids, and anti-viral compounds are non-limiting examples of pharmaceutical agents that can be combined with or used in conjunction with the nucleic acid molecules (e.g. siNA molecules) of the instant invention. The use of ribavirin and oseltamivir are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (e.g. siNA molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (e.g. siNA molecules) and are hence within the scope of the instant invention.

Example 11: Interferons

Interferons represent a non-limiting example of a class of compounds that can be used in conjunction with the siNA molecules of the invention for treating the diseases and/or conditions described herein. Type I interferons (IFN) are a class of natural cytokines that includes a family of greater than 25 IFN- α (Pesta, 1986, *Methods Enzymol.* 119, 3-14) as well as IFN- β , and IFN- ω . Although evolutionarily derived from the same gene (Diaz *et al.*, 1994, *Genomics* 22, 540-552), there are many differences in the primary sequence of these molecules, implying an evolutionary divergence in biologic activity. All type I IFN share a common pattern of biologic effects that begin with binding of the IFN to the cell surface receptor (Pfeffer & Strulovici, 1992, Transmembrane secondary messengers for IFN- α/β . In: *Interferon. Principles and*

Medical Applications., S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds. 151-160). Binding is followed by activation of tyrosine kinases, including the Janus tyrosine kinases and the STAT proteins, which leads to the production of several IFN-stimulated gene products (Johnson *et al.*, 1994, *Sci. Am.* 270, 68-75). The IFN-stimulated gene products are responsible for the pleiotropic biologic effects of type I IFN, including antiviral, antiproliferative, and immunomodulatory effects, cytokine induction, and HLA class I and class II regulation (Pestka *et al.*, 1987, *Annu. Rev. Biochem* 56, 727). Examples of IFN-stimulated gene products include 2-5-oligoadenylate synthetase (2-5 OAS), β_2 -microglobulin, neopterin, p68 kinases, and the Mx protein (Chebath & Revel, 1992, The 2-5 A system: 2-5 A synthetase, isospecies and functions. In: *Interferon. Principles and Medical Applications*, S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Jr. Fleischmann, T.K. Jr Hughes, G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds., pp. 225-236; Samuel, 1992, The RNA-dependent P1/eIF-2 α protein kinase. In: *Interferon. Principles and Medical Applications*. S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 237-250; Horisberger, 1992, MX protein: function and Mechanism of Action. In: *Interferon. Principles and Medical Applications*. S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 215-224). Although all type I IFN have similar biologic effects, not all the activities are shared by each type I IFN, and in many cases, the extent of activity varies quite substantially for each IFN subtype (Fish *et al.*, 1989, *J. Interferon Res.* 9, 97-114; Ozes *et al.*, 1992, *J. Interferon Res.* 12, 55-59). More specifically, investigations into the properties of different subtypes of IFN- α and molecular hybrids of IFN- α have shown differences in pharmacologic properties (Rubinstein, 1987, *J. Interferon Res.* 7, 545-551). These pharmacologic differences can arise from as few as three amino acid residue changes (Lee *et al.*, 1982, *Cancer Res.* 42, 1312-1316).

Eighty-five to 166 amino acids are conserved in the known IFN- α subtypes. Excluding the IFN- α pseudogenes, there are approximately 25 known distinct IFN- α subtypes. Pairwise comparisons of these nonallelic subtypes show primary sequence

differences ranging from 2% to 23%. In addition to the naturally occurring IFNs, a non-natural recombinant type I interferon known as consensus interferon (CIFN) has been synthesized as a therapeutic compound (Tong *et al.*, 1997, *Hepatology* 26, 747-754).

Interferon is currently in use for at least 12 different indications, including
5 infectious and autoimmune diseases and cancer (Borden, 1992, *N. Engl. J. Med.* 326, 1491-1492). For autoimmune diseases, IFN has been utilized for treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease. For treatment of cancer, IFN has been used alone or in combination with a number of different compounds. Specific types of cancers for which IFN has been used include squamous cell
10 carcinomas, melanomas, hypernephromas, hemangiomas, hairy cell leukemia, and Kaposi's sarcoma. In the treatment of infectious diseases, IFNs increase the phagocytic activity of macrophages and cytotoxicity of lymphocytes and inhibits the propagation of cellular pathogens. Specific indications for which IFN has been used as treatment include hepatitis B, human papillomavirus types 6 and 11 (i.e. genital warts) (Leventhal
15 *et al.*, 1991, *N Engl J Med* 325, 613-617), chronic granulomatous disease, and SARS virus.

Pegylated interferons, i.e., interferons conjugated with polyethylene glycol (PEG), have demonstrated improved characteristics over interferon. Advantages incurred by PEG conjugation can include an improved pharmacokinetic profile compared to
20 interferons lacking PEG, thus imparting more convenient dosing regimes, improved tolerance, and improved antiviral efficacy. Such improvements have been demonstrated in clinical studies of both polyethylene glycol interferon alfa-2a (PEGASYS, Roche) and polyethylene glycol interferon alfa-2b (VIRAFERON PEG, PEG-INTRON, Enzon/Schering Plough).

25 siNA molecules in combination with interferons and polyethylene glycol interferons have the potential to improve the effectiveness of treatment of SARS or any of the other indications discussed above. siNA molecules targeting RNAs associated with SARS virus infection can be used individually or in combination with other therapies such as interferons and polyethylene glycol interferons and to achieve
30 enhanced efficacy.

Example 12: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls,

synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches

one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Table I: SARS virus Accession Numbers

5 LOCUS NC_004718 29736 bp ss-RNA linear VRL 15-APR-2003
DEFINITION SARS coronavirus, complete genome.
ACCESSION NC_004718

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Table II: SARS siNA and Target Sequences

SARS CoV NC 004718

Pos	Seq	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
3	ACCCAGGAAAGGCAAGCA	1	3	ACCCAGGAAAGGCAAGCA	1	21	UGGUUGGCUUUUCCUGGGU	1652
21	AACCCUGAUCUCUUGUAGA	2	21	AACCCUGAUCUCUUGUAGA	2	39	UCUUAAGAGUUCGAGGUU	1653
39	AUCUGUUCUCUUAACGAAC	3	39	AUCUGUUCUCUUAACGAAC	3	57	GUUCGUUUAGAGAACAGAU	1654
57	CUUUAAAUCUGUGUAGCU	4	57	CUUUAAAUCUGUGUAGCU	4	75	AGCUACACAGAUUUUAAAG	1655
75	UGUGGUCUGGUGCAUGCC	5	75	UGUGGUCUGGUGCAUGCC	5	93	GGCAUGCAGCCGAGCGACA	1656
93	CUAGUGCACCUCACGAGUA	6	93	CUAGUGCACCUCACGAGUA	6	111	UACUGCGUAGGUGCACUAG	1657
111	AUAAACAUAUAUUUUUU	7	111	AUAAACAUAUAUUUUUU	7	129	AAAAUUUAUUUGUUUUU	1658
129	UACUGUGCUUGACAGAAA	8	129	UACUGUGCUUGACAGAAA	8	147	UUUUUUUUAACACGACGUA	1659
147	ACGAGUAACUCGUCCUCU	9	147	ACGAGUAACUCGUCCUCU	9	165	AGAGGACGAGUUUACUGU	1660
165	UUCUGCAGACUGCUUACGG	10	165	UUCUGCAGACUGCUUACGG	10	183	CCGUAAAGCAGUCUGCAGAA	1661
183	GUUUCGUCGUGUUGCAGU	11	183	GUUUCGUCGUGUUGCAGU	11	201	ACUGCAACACGCGGAAAC	1662
201	UCGAUCAUCAGCAUCCUA	12	201	UCGAUCAUCAGCAUCCUA	12	219	UAGGUUGCUUGAUUGCA	1663
219	AGGUUUCGUCGGGUGUGA	13	219	AGGUUUCGUCGGGUGUGA	13	237	UCACACCGGACGAAACCU	1664
237	ACCGAAAGGUAGAUGGAG	14	237	ACCGAAAGGUAGAUGGAG	14	255	CUCCAUCUUAACCUUUCGGU	1665
255	GAGCCUUGUUCUUGGUGUC	15	255	GAGCCUUGUUCUUGGUGUC	15	273	GACACCAAGAAACAAGGCUC	1666
273	CAACGAGAAACACACGUC	16	273	CAACGAGAAACACACGUC	16	291	GACGUGUGUUUUCUGGUG	1667
291	CCAAUCUCAGUUUGCUGUC	17	291	CCAAUCUCAGUUUGCUGUC	17	309	GACAGGCAAAACUGAGUUG	1668
309	CCUUCAGGUUAGAGACGUG	18	309	CCUUCAGGUUAGAGACGUG	18	327	CACGUCUCUUAACCUAGAG	1669
327	GCUAGUGCGUGGUUCGCGG	19	327	GCUAGUGCGUGGUUCGCGG	19	345	CCCGAAGCCACGCAUAGC	1670
345	GGACUCUGUGGAGAGGCC	20	345	GGACUCUGUGGAGAGGCC	20	363	GGCCUCUCCACAGAGUCC	1671
363	CCUACUGGAGGACGUGAA	21	363	CCUACUGGAGGACGUGAA	21	381	UUCACGUGCCUCCGAGUAG	1672
381	ACACCUCAAAAUGGCACU	22	381	ACACCUCAAAAUGGCACU	22	399	AGUGCCAUUUUUAGGUGU	1673
399	UUGUGUCUAGUAGAGCUG	23	399	UUGUGUCUAGUAGAGCUG	23	417	CAGCUCUACUAGACCAAA	1674
417	GGAAAAGGCGUACUGCCC	24	417	GGAAAAGGCGUACUGCCC	24	435	GGGAGUACGCGUUUUUCC	1675
435	CCAGCUUGAACAGCCCUAU	25	435	CCAGCUUGAACAGCCCUAU	25	453	AUAGGCGUUAUAAAGCUGG	1676
453	UGUGUUCUUAACGCUUCU	26	453	UGUGUUCUUAACGCUUCU	26	471	AGAAGCUUUAUAGAACACA	1677
471	UGAUGCCUUAAGCACCACU	27	471	UGAUGCCUUAAGCACCACU	27	489	AUUGGUGCUUAAGGCAUCA	1678
489	UCACGGCCACAGGUCGUU	28	489	UCACGGCCACAGGUCGUU	28	507	AACGACCUUGUGGCGUGA	1679
507	UGAGCUGGUUGCAGAAUG	29	507	UGAGCUGGUUGCAGAAUG	29	525	CAUUUCUGCAACACGCUCA	1680
525	GGACGGCAUUCAGUACGGU	30	525	GGACGGCAUUCAGUACGGU	30	543	ACCGUACUUAUACCGGUCC	1681
543	UCGUAGCGGUUAUACACUG	31	543	UCGUAGCGGUUAUACACUG	31	561	CAGUGUUAUACCGUACGA	1682
561	GGGAGUACUCUGGCCACAU	32	561	GGGAGUACUCUGGCCACAU	32	579	AUGUGGACGAGUACUCCC	1683
579	UGUGGGCGAAACCCCAUUU	33	579	UGUGGGCGAAACCCCAUUU	33	597	AAUUGGGUUUUCGCCACA	1684
597	UGCAUACCGCAUUGUUCUU	34	597	UGCAUACCGCAUUGUUCUU	34	615	AAGAACAUGCGGUAGUCA	1685
615	UCUUCGUAGAACGUGUAU	35	615	UCUUCGUAGAACGUGUAU	35	633	AUUAACCGUUCUUAAGGA	1686
633	UAAGGGAGCGGUGGUGCAU	36	633	UAAGGGAGCGGUGGUGCAU	36	651	AUGACCACCGGUGCCUUA	1687

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651	UAGCUAUGGCAUCGACUA	37	651	UAGCUAUGGCAUCGACUA	37	669	UAGCUAUGGCAUCGACUA	1688
689	AAAGUCUUAUGACUAGGU	38	669	AAAGUCUUAUGACUAGGU	38	687	ACCUAAGUCUAUAGACUUA	1689
687	UGACGAGCUUGGCACUGAU	39	687	UGACGAGCUUGGCACUGAU	39	705	AUCAGUCCAAAGCUCGUA	1690
705	UCCCAUUGAAGAUUAUGAA	40	705	UCCCAUUGAAGAUUAUGAA	40	723	UUCAUAAUUCUCAAUGGA	1691
723	ACAAAACUGGAACACUAAG	41	723	ACAAAACUGGAACACUAAG	41	741	CUUAGUGUUCGAGUUUUGU	1692
741	GCAUGGCGAGUGGACACUC	42	741	GCAUGGCGAGUGGACACUC	42	759	GAGUGCACCAGUGCCAUGC	1693
759	CCGUGAACUCACUCGUGAG	43	759	CCGUGAACUCACUCGUGAG	43	777	CUCAGGUGAGUUCACCGG	1694
777	GCUCAAUGGAGUGGACGUC	44	777	GCUCAAUGGAGUGGACGUC	44	795	GACUGCACCUCGUAUUGAGC	1695
795	CACUCGCUAUGUGGACAAAC	45	795	CACUCGCUAUGUGGACAAAC	45	813	GUUGUCGACAUAGCGAGUG	1696
813	CAUUUCUGUGGCGCCAGAU	46	813	CAUUUCUGUGGCGCCAGAU	46	831	AUCUGGGCCACAGAAAUG	1697
831	UGGGUACCCUCUUGAUUGC	47	831	UGGGUACCCUCUUGAUUGC	47	849	GCAUCAAAGAGGGUACCCA	1698
849	CAUCAAAGAUUUUCUGCA	48	849	CAUCAAAGAUUUUCUGCA	48	867	UGCGAGAAAUCUUUUGAUG	1699
867	ACGCGGGGCAAGUCAUUG	49	867	ACGCGGGGCAAGUCAUUG	49	885	CAUUGACUUGCCCGCGCGU	1700
885	GUGCACUCUUCGGAACAA	50	885	GUGCACUCUUCGGAACAA	50	903	UUGUUCGGAAGAGUGGCAC	1701
903	ACUUGAUUACUAGCUGC	51	903	ACUUGAUUACUAGCUGC	51	921	CGACUCGUAUUAUCAAGU	1702
921	GAAGAGAGUGUUCUACUGC	52	921	GAAGAGAGUGUUCUACUGC	52	939	GCAGUAGACCCUCUCUUC	1703
939	CUGCCGUGACAUAGAGCAU	53	939	CUGCCGUGACAUAGAGCAU	53	957	AUGCUCAUGGUCACGGCAG	1704
957	UGAAAUUGCCUGGUUCACU	54	957	UGAAAUUGCCUGGUUCACU	54	975	AGUAAACAGGCAUUAUCA	1705
975	UGAGCGCUCUGAUAGAGC	55	975	UGAGCGCUCUGAUAGAGC	55	993	GCUCUUAUCAGAGCGCUCA	1706
993	CAGCAGACCCAGACACCC	56	993	CAGCAGACCCAGACACCC	56	1011	GGGUGUCUGGUGCUGCUGAG	1707
1011	CUUCGAAUUAAGAGUGCC	57	1011	CUUCGAAUUAAGAGUGCC	57	1029	GGCAGCUUAAUUUUCGAAG	1708
1029	CAAGAAUUAAGAGUGCC	58	1029	CAAGAAUUAAGAGUGCC	58	1047	GAAAGUGUCAAUUAUUG	1709
1047	CAAAGGGGAUUGCCCAAAG	59	1047	CAAAGGGGAUUGCCCAAAG	59	1065	CUUUGGCAUUCUCCUUG	1710
1065	GUUUGUUAUCCUUAAC	60	1065	GUUUGUUAUCCUUAAC	60	1083	GUUAGAGGAAACACAAAC	1711
1083	CUCAAAAGUCAAAGUCAU	61	1083	CUCAAAAGUCAAAGUCAU	61	1101	AUAGACUUUGACUUUUGAG	1712
1101	UCAACCCAGUGUUGAAAG	62	1101	UCAACCCAGUGUUGAAAG	62	1119	CUUUUCAAACAGUGGUUGA	1713
1119	GAUAAAGACUGAGGUGUUC	63	1119	GAUAAAGACUGAGGUGUUC	63	1137	GAAACCCUACAGUCUUUUC	1714
1137	CAUGGGGCGUAUACGCUCU	64	1137	CAUGGGGCGUAUACGCUCU	64	1155	AGAGCGUAUACGCCCAUG	1715
1155	UGUGUACCCUUGUUGCAUCU	65	1155	UGUGUACCCUUGUUGCAUCU	65	1173	AGAUCAAACAGGGUACACA	1716
1173	UCCACAGGAGUGUAACAAU	66	1173	UCCACAGGAGUGUAACAAU	66	1191	AUUGUACACUCCUGGGA	1717
1191	UAUGCACUUGUCUACCUUG	67	1191	UAUGCACUUGUCUACCUUG	67	1209	CAAGGUAGACAAGUGCAUA	1718
1209	GAUGAAUUGUAUUAUUGC	68	1209	GAUGAAUUGUAUUAUUGC	68	1227	GCAUUAUUAUUAUUAUUAUC	1719
1227	CGAUGAAGUUUAUGGCAG	69	1227	CGAUGAAGUUUAUGGCAG	69	1245	CUGCAUGAAACUUAUUAUCG	1720
1245	GACGUGCGACUUAUUGAAA	70	1245	GACGUGCGACUUAUUGAAA	70	1263	UUUGCAAGAGUCGACGUC	1721
1263	AGCCACUUGUGAACAUUGU	71	1263	AGCCACUUGUGAACAUUGU	71	1281	ACAAUUAUUAUUAUUAUUAUC	1722
1281	UGGCACUGAAAUUUUUGUU	72	1281	UGGCACUGAAAUUUUUGUU	72	1299	AACUAAUUUAUUAUUAUUAUC	1723
1299	UAUUGAAGGACCUUACUACA	73	1299	UAUUGAAGGACCUUACUACA	73	1317	UGUAUGAGGUCCUUAUUAUC	1724
1317	UAUUGGGUAGUAGUAAUUG	74	1317	UAUUGGGUAGUAGUAAUUG	74	1335	AGUAGGUAGGUACCCACAU	1725
1335	UAUUGGUGUAGUAGUAAUUG	75	1335	UAUUGGUGUAGUAGUAAUUG	75	1353	CAUUUACACUACAGAUUAU	1726
1353	GCGAUGUCCUGCCUGUCAA	76	1353	GCGAUGUCCUGCCUGUCAA	76	1371	UUGACAGGCGAGGACGAGG	1727
1371	AGACCCAGAGAUUGGACCU	77	1371	AGACCCAGAGAUUGGACCU	77	1389	AGGUCAAUUCUUGGUGUCU	1728
1389	UGAGCAUAGUGUUGCAGAU	78	1389	UGAGCAUAGUGUUGCAGAU	78	1407	AUCUGCAACACUUAUGCUCA	1729

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1407	UUAUCACAACCCACUCACAAAC	79	1407	UUAUCACAACCCACUCACAAAC	79	1425	GUUUGAGUGGUUGUGUAUA	1730
1425	CAUUGAAACUCGACUCCGC	80	1425	CAUUGAAACUCGACUCCGC	80	1443	GCGGAGUCGAGUUUCAAUG	1731
1443	CAAGGGAGGAGGACUAGA	81	1443	CAAGGGAGGAGGACUAGA	81	1461	UCUAGUCCUACCUCCCUUG	1732
1461	AUGUUUUGGAGGUGUGUG	82	1461	AUGUUUUGGAGGUGUGUG	82	1479	CACACAGCUCACAAACAUC	1733
1479	GUUUGCCUAUUGGCGUC	83	1479	GUUUGCCUAUUGGCGUC	83	1497	GCAGCCAAUAUAGGCAAC	1734
1497	CUAUAAUAGCGGCGCUAC	84	1497	CUAUAAUAGCGGCGCUAC	84	1515	GUAGGCACGCUUUAUUAUG	1735
1515	CUGGUGUCCUGGUGCUAGU	85	1515	CUGGUGUCCUGGUGCUAGU	85	1533	ACUAGCAGGAGAAACCCAG	1736
1533	UGCUGAUUUGGUCACGCG	86	1533	UGCUGAUUUGGUCACGCG	86	1551	GCCUGAGCCAAUAUACGCA	1737
1551	CCAUACUGGCAUUAUCUGGU	87	1551	CCAUACUGGCAUUAUCUGGU	87	1569	ACCAGUAUUGCCAGUAUGG	1738
1569	UGACAAUUGGAGACCUUG	88	1569	UGACAAUUGGAGACCUUG	88	1587	CAAGGUCUCCACAUUGUCA	1739
1587	GAUAGGAGGACUCCUUGAG	89	1587	GAUAGGAGGACUCCUUGAG	89	1605	CUCAAGGAGAUCCUCAUUC	1740
1605	GAUACUGAGUCGUGAACGU	90	1605	GAUACUGAGUCGUGAACGU	90	1623	ACGUUCACGACUCAGUAUC	1741
1623	UGUUAACAUAACAUUGUU	91	1623	UGUUAACAUAACAUUGUU	91	1641	AACAUGUUAUUGUUAACA	1742
1641	UGGCGAUUUCAUUAUGAAU	92	1641	UGGCGAUUUCAUUAUGAAU	92	1659	AUCAAUUGAAAUUCGCCA	1743
1659	UGAAGAGGUUGCCAUCAUU	93	1659	UGAAGAGGUUGCCAUCAUU	93	1677	AUGAUGGCAACCCUUCUCA	1744
1677	UUUGGCAUUCUUCUCUGCU	94	1677	UUUGGCAUUCUUCUCUGCU	94	1695	AGCAGAGAAAGAUCCCAAA	1745
1695	UUCUACAAGUCCCUUAUU	95	1695	UUCUACAAGUCCCUUAUU	95	1713	AUAAGGCACUUGUAGAA	1746
1713	UGACACUAUAAAGAGUCUU	96	1713	UGACACUAUAAAGAGUCUU	96	1731	AAGACUCUUUAUAGUGUCA	1747
1731	UGAUUACAAGUCUUUCAA	97	1731	UGAUUACAAGUCUUUCAA	97	1749	UUUGAAAGACUUGUAUUA	1748
1749	AACCAUUGUUGAGUCCUGC	98	1749	AACCAUUGUUGAGUCCUGC	98	1767	GCAGGACUCACCAUUGGUU	1749
1767	CGGUAACUAUAAAGUUAAC	99	1767	CGGUAACUAUAAAGUUAAC	99	1785	GGUAUUAUUAUAGUUAACCG	1750
1785	CAAGGGAAGCCCGUAAA	100	1785	CAAGGGAAGCCCGUAAA	100	1803	UUUUAACGGCUUUCUCCUUG	1751
1803	AGGUGCUUGGAACAUUGGA	101	1803	AGGUGCUUGGAACAUUGGA	101	1821	UCCAUGUUAUUAAGCACCU	1752
1821	ACAACAGAUCAUGUUUA	102	1821	ACAACAGAUCAUGUUUA	102	1839	UAAACUGAUCUCUGUUGU	1753
1839	AACACACUUGUGUUGUUU	103	1839	AACACACUUGUGUUGUUU	103	1857	AAACCCACACAGUGGUGU	1754
1857	UCCUUCACAGGCGUGUGU	104	1857	UCCUUCACAGGCGUGUGU	104	1875	ACCAGCAGCCUGUGAGGGA	1755
1875	UGUUAUCAGAUCAUUAUU	105	1875	UGUUAUCAGAUCAUUAUU	105	1893	AAAAUUGAUCUGAUAAACA	1756
1893	UGCGGCACACUUGAUGCA	106	1893	UGCGGCACACUUGAUGCA	106	1911	UGCAUCAAUGUGUGCGCGCA	1757
1911	AGCAAACCCACUUAUCCU	107	1911	AGCAAACCCACUUAUCCU	107	1929	AGGAUUGAGUGGUUUGCU	1758
1929	UGAUUUGCAAAGAGCAGCU	108	1929	UGAUUUGCAAAGAGCAGCU	108	1947	AGUGUCUUAUUGCAAUUA	1759
1947	UGUACCAUUAUUGAUGGU	109	1947	UGUACCAUUAUUGAUGGU	109	1965	ACCAUCAAUGGCAUUA	1760
1965	UAUUUCUGAACAGUCAUUA	110	1965	UAUUUCUGAACAGUCAUUA	110	1983	UAAUGACUGUUCAGAAUUA	1761
1983	ACGUCUUGCGACGCCAUG	111	1983	ACGUCUUGCGACGCCAUG	111	2001	CAUGGCGUCGACAAGACGU	1762
2001	GGUUUAUUAUUCAGACCGU	112	2001	GGUUUAUUAUUCAGACCGU	112	2019	CAGGUCUGAAGUAUAAACC	1763
2019	GCUCACCAACAGUGUCAUU	113	2019	GCUCACCAACAGUGUCAUU	113	2037	AAUGACACUGUUGGUGAGC	1764
2037	UAUUAUGGCAUUAUGUAACU	114	2037	UAUUAUGGCAUUAUGUAACU	114	2055	AGUUAUUAUUGGCAUUA	1765
2055	UGGUGGUCUUGUAACAACAG	115	2055	UGGUGGUCUUGUAACAACAG	115	2073	CUGUUGUAACAAGACCAACA	1766
2073	GACUUCUCAGUGUUGUCU	116	2073	GACUUCUCAGUGUUGUCU	116	2091	AGACAACCCACUGAGAAAGUC	1767
2091	UAUUCUUUUGGCGACUACU	117	2091	UAUUCUUUUGGCGACUACU	117	2109	AGUAGUCCCAAAAGAUUA	1768
2109	UGUUGAAAACUCAGGCCU	118	2109	UGUUGAAAACUCAGGCCU	118	2127	AGGCGUGAGUUUUAACAACA	1769
2127	UAUCUUUGAAUUGGUAUGAG	119	2127	UAUCUUUGAAUUGGUAUGAG	119	2145	CUCAUCCAUUCAAAGAUUA	1770
2145	GGCGAAACUUAUGUCAGGA	120	2145	GGCGAAACUUAUGUCAGGA	120	2163	UCCUGCACUAAGUUUCGCC	1771

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2163	AGUUGAAUUUCUCAAAGGAU	121	2163	AGUUGAAUUUCUCAAAGGAU	121	2181	AUCCUUGAGAAAUUUAACAU	1772
2181	UGCUUGGGAGAUUUCUCAA	122	2181	UGCUUGGGAGAUUUCUCAA	122	2199	UUUGAGAAUUCUCCCAAGCA	1773
2199	AUUUCUCAUUAACAGGUGU	123	2199	AUUUCUCAUUAACAGGUGU	123	2217	AACACCCUGUAUAGAGAAU	1774
2217	UUUUGACAUUGCUAAGGUGU	124	2217	UUUUGACAUUGCUAAGGUGU	124	2235	ACCCUUGACGAGUUAACAA	1775
2235	UCAAAUACAGGUGUUAUUA	125	2235	UCAAAUACAGGUGUUAUUA	125	2253	UGAAGCAACCCUGUAUUGA	1776
2253	AGAUACAUAACAGGUAUUGU	126	2253	AGAUACAUAACAGGUAUUGU	126	2271	ACAAUCCUUGAGUUAUUCU	1777
2271	UGUAAAUGCUUAUUAUUAU	127	2271	UGUAAAUGCUUAUUAUUAU	127	2289	AUCAUUGAGCAUUAUUA	1778
2289	UGUUGUUAACAGGCACUC	128	2289	UGUUGUUAACAGGCACUC	128	2307	GAGUCCUUGUUAACAAACA	1779
2307	CGAAUUGCAUUAUUAUUA	129	2307	CGAAUUGCAUUAUUAUUA	129	2325	UAGUCAAUUGCAUUAUUCG	1780
2325	AGUCACUAUCGCGGCGCA	130	2325	AGUCACUAUCGCGGCGCA	130	2343	UGCGCAGCGAUAGUGACU	1781
2343	AAAGUUGCGAUACACUAC	131	2343	AAAGUUGCGAUACACUAC	131	2361	GUUGAGUAGCGCAACUUAU	1782
2361	CUUAGGUGAAGUCUUAUC	132	2361	CUUAGGUGAAGUCUUAUC	132	2379	GAUGAAGACUUAACCUAAG	1783
2379	CGCUCAAAGCAAGGACU	133	2379	CGCUCAAAGCAAGGACU	133	2397	GAUCCUUGCUUUGAGCG	1784
2397	UUACCGUCAGUUAUACGU	134	2397	UUACCGUCAGUUAUACGU	134	2415	ACGUUAACACUGACGUAA	1785
2415	UGGCAAGGAGCAGCUGCAA	135	2415	UGGCAAGGAGCAGCUGCAA	135	2433	UUGCAGCUGCUCCUUGCCA	1786
2433	ACUACUCAUGCCUCUUAAG	136	2433	ACUACUCAUGCCUCUUAAG	136	2451	CUUAAAGGCGAUAGUAGU	1787
2451	GGCACCAAAAGAAUAACC	137	2451	GGCACCAAAAGAAUAACC	137	2469	GGUUAUCUUAUUGGUGCC	1788
2469	CUUUCUUAAGGUGUAUUA	138	2469	CUUUCUUAAGGUGUAUUA	138	2487	UGAAUACCUUAACGAAAG	1789
2487	ACAUGACACAGUUAUUA	139	2487	ACAUGACACAGUUAUUA	139	2505	GGUAAGUACUGUGUUAUUA	1790
2505	CUCUGAGGAGGUGUUAUUA	140	2505	CUCUGAGGAGGUGUUAUUA	140	2523	GAGAAUACCUUCCUUCAGAG	1791
2523	CAAGAACGGUUAUUAUUA	141	2523	CAAGAACGGUUAUUAUUA	141	2541	UUCGAGUUAUUAUUAUUA	1792
2541	AGCUCUUAUUAUUAUUA	142	2541	AGCUCUUAUUAUUAUUA	142	2559	AACGGGCGUCCGAGUGCU	1793
2559	UGAUAGCUUAUUAUUAUUA	143	2559	UGAUAGCUUAUUAUUAUUA	143	2577	UCCAUUUGUGAAGCUUAUA	1794
2577	AGCUAUCGUGGACACCA	144	2577	AGCUAUCGUGGACACCA	144	2595	UGGUGUGCGGACGUAUAGCU	1795
2595	AGUCUGUGUUAUUAUUAUUA	145	2595	AGUCUGUGUUAUUAUUAUUA	145	2613	GAGGCCAUUUAACACAGACU	1796
2613	CAUGCUCUUAAGAUUAAG	146	2613	CAUGCUCUUAAGAUUAAG	146	2631	CUUAAUCUCUUAAGAGCAUG	1797
2631	GGACAAAGAAUUAUUAUUA	147	2631	GGACAAAGAAUUAUUAUUA	147	2649	GCAGUAUUGUUAUUAUUA	1798
2649	CGCAUUGUCUUAUUAUUA	148	2649	CGCAUUGUCUUAUUAUUA	148	2667	UAAACCCAGGAGACAAUUGCG	1799
2667	ACUGGCUAUAUUAUUAUUA	149	2667	ACUGGCUAUAUUAUUAUUA	149	2685	GACAUUUGUUAUUAUUAUUA	1800
2685	CUUUCGCUUAUUAUUAUUA	150	2685	CUUUCGCUUAUUAUUAUUA	150	2703	ACCCCUUUAUUAUUAUUA	1801
2703	UGCACCAUUAUUAUUAUUA	151	2703	UGCACCAUUAUUAUUAUUA	151	2721	UACACCUUUAUUAUUAUUA	1802
2721	AACCUUUGGAGAAUUAUUA	152	2721	AACCUUUGGAGAAUUAUUA	152	2739	AGUAUCUUAUUAUUAUUA	1803
2739	UGUUGGGAAGUUAUUAUUA	153	2739	UGUUGGGAAGUUAUUAUUA	153	2757	ACCUUGAACUUAUUAUUA	1804
2757	UUAACAAGAAUUAUUAUUA	154	2757	UUAACAAGAAUUAUUAUUA	154	2775	GAUUCACAUUAUUAUUA	1805
2775	CACAUUUGAGCUUAUUAUUA	155	2775	CACAUUUGAGCUUAUUAUUA	155	2793	UUAUCAAGCUCUUAUUA	1806
2793	ACGUGUUAUUAUUAUUAUUA	156	2793	ACGUGUUAUUAUUAUUAUUA	156	2811	AAGCACUUAUUAUUAUUA	1807
2811	UUAUGAAAGUUAUUAUUA	157	2811	UUAUGAAAGUUAUUAUUA	157	2829	GACAGAGCACUUAUUAUUA	1808
2829	CUACACUUAUUAUUAUUAUUA	158	2829	CUACACUUAUUAUUAUUAUUA	158	2847	ACCGGAUUAUUAUUAUUA	1809
2847	UACCGAAGUUAUUAUUAUUA	159	2847	UACCGAAGUUAUUAUUAUUA	159	2865	AAACUUAUUAUUAUUAUUA	1810
2865	UGCAUGUUAUUAUUAUUAUUA	160	2865	UGCAUGUUAUUAUUAUUAUUA	160	2883	CUUCUUAUUAUUAUUAUUA	1811
2883	GGCUGUUAUUAUUAUUAUUA	161	2883	GGCUGUUAUUAUUAUUAUUA	161	2901	UAAAGUUAUUAUUAUUAUUA	1812
2901	ACAACCAUUAUUAUUAUUA	162	2901	ACAACCAUUAUUAUUAUUA	162	2919	GAGAUUAUUAUUAUUAUUA	1813

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2919	CCUACCAACAUGGGUAAU	163	CCUACCAACAUGGGUAAU	163	2919	CCUACCAACAUGGGUAAU	163	2937	AAUACCAUGUUGGUAAGG	1814
2937	UGAUCUUGAGAGUGGAGU	164	UGAUCUUGAGAGUGGAGU	164	2937	UGAUCUUGAGAGUGGAGU	164	2955	ACUCCACUACAAGAUCA	1815
2955	UGAGCUACAUCUACUUA	165	UGAGCUACAUCUACUUA	165	2955	UGAGCUACAUCUACUUA	165	2973	UAAGUAGAUUGAGCUACA	1816
2973	AUUUGAUGAGUGGUGAA	166	AUUUGAUGAGUGGUGAA	166	2973	AUUUGAUGAGUGGUGAA	166	2991	UUCACCAUGAUCAUCAAU	1817
2991	AGAAACUUUUCAUCACGU	167	AGAAACUUUUCAUCACGU	167	2991	AGAAACUUUUCAUCACGU	167	3009	ACGUGAUGAAAGAUUUCU	1818
3009	UAUGAUUUGUCCUUAUAC	168	UAUGAUUUGUCCUUAUAC	168	3009	UAUGAUUUGUCCUUAUAC	168	3027	GUAAAGGAACAUAUAUA	1819
3027	CCUCCAGAUGAGGAAGAA	169	CCUCCAGAUGAGGAAGAA	169	3027	CCUCCAGAUGAGGAAGAA	169	3045	UUAUCCUACAUCUGGAGG	1820
3045	AGAGGACGAUGCAGAGUGU	170	AGAGGACGAUGCAGAGUGU	170	3045	AGAGGACGAUGCAGAGUGU	170	3063	ACACUCUGCAUCUGCCUCU	1821
3063	UGAGGAAGAGAAAUUGAU	171	UGAGGAAGAGAAAUUGAU	171	3063	UGAGGAAGAGAAAUUGAU	171	3081	AUCAUUUCUUCUCCUCA	1822
3081	UGAAACCUUGAGACAUGAG	172	UGAAACCUUGAGACAUGAG	172	3081	UGAAACCUUGAGACAUGAG	172	3099	CUCAUUUCACAGGUUUA	1823
3099	GUACGGUACAGAGGAUGAU	173	GUACGGUACAGAGGAUGAU	173	3099	GUACGGUACAGAGGAUGAU	173	3117	AUCAUCUCUGUACCGUAC	1824
3117	UUUAACAAGGUCUCCUCUG	174	UUUAACAAGGUCUCCUCUG	174	3117	UUUAACAAGGUCUCCUCUG	174	3135	CAGAGGAGACCUUGAUAA	1825
3135	GGAAUUUGGUGCCUCAGCU	175	GGAAUUUGGUGCCUCAGCU	175	3135	GGAAUUUGGUGCCUCAGCU	175	3153	AGCUGAGGACCAAUUCC	1826
3153	UGAAACAAGUUGAGUAG	176	UGAAACAAGUUGAGUAG	176	3153	UGAAACAAGUUGAGUAG	176	3171	CUCAUCUGCAUCUGUUA	1827
3171	GGAGGAAGAGGGAAGAC	177	GGAGGAAGAGGGAAGAC	177	3171	GGAGGAAGAGGGAAGAC	177	3189	GUCUCCUCUUCUUCUCC	1828
3189	CUGGCUUGGAUGAUACU	178	CUGGCUUGGAUGAUACU	178	3189	CUGGCUUGGAUGAUACU	178	3207	AGUAUAUCUCCAGCCAG	1829
3207	UGAGCAUUCAGAGAUUGAG	179	UGAGCAUUCAGAGAUUGAG	179	3207	UGAGCAUUCAGAGAUUGAG	179	3225	CUCAUCUCUGAUUGCUCA	1830
3225	GCCAGAACCAAGACCUACA	180	GCCAGAACCAAGACCUACA	180	3225	GCCAGAACCAAGACCUACA	180	3243	UGUAGGUUCUGUUCUGGC	1831
3243	ACCUGAAGAACCCAGUUAU	181	ACCUGAAGAACCCAGUUAU	181	3243	ACCUGAAGAACCCAGUUAU	181	3261	AUUAACUGGUUCUUCAGGU	1832
3261	UCAGUUACUGGUUAUUA	182	UCAGUUACUGGUUAUUA	182	3261	UCAGUUACUGGUUAUUA	182	3279	UAAUAACCAAGUAAACUGA	1833
3279	AAACUUACUGACAAGUUU	183	AAACUUACUGACAAGUUU	183	3279	AAACUUACUGACAAGUUU	183	3297	AAAUUUGCAGUAAAGUUU	1834
3297	UGCCAUUAAUUGUUGAC	184	UGCCAUUAAUUGUUGAC	184	3297	UGCCAUUAAUUGUUGAC	184	3315	GUAACACAUUUAUUGGCA	1835
3315	CAUCGUUAAAGGAGCACAA	185	CAUCGUUAAAGGAGCACAA	185	3315	CAUCGUUAAAGGAGCACAA	185	3333	UUGUGCCUUAUACCAUG	1836
3333	AAGUGCUAAUCCUUGUG	186	AAGUGCUAAUCCUUGUG	186	3333	AAGUGCUAAUCCUUGUG	186	3351	CACAUAAGGAUUAAGCAU	1837
3351	GAUUGUAAUUGCUGUAAC	187	GAUUGUAAUUGCUGUAAC	187	3351	GAUUGUAAUUGCUGUAAC	187	3369	GUUAGCAGCAUUAUACAUC	1838
3369	CAUACACCUUGAAACAUGGU	188	CAUACACCUUGAAACAUGGU	188	3369	CAUACACCUUGAAACAUGGU	188	3387	ACCAUUGUUCAGGUUAUG	1839
3387	UGGUGGUGUAGCAGGUGCA	189	UGGUGGUGUAGCAGGUGCA	189	3387	UGGUGGUGUAGCAGGUGCA	189	3405	UGCACCUUGUACACCA	1840
3405	ACUCAACAAGGCAACCAU	190	ACUCAACAAGGCAACCAU	190	3405	ACUCAACAAGGCAACCAU	190	3423	AUUGGUUCCUUGUUGAGU	1841
3423	UGGUGGUGUAGCAGGUGCA	191	UGGUGGUGUAGCAGGUGCA	191	3423	UGGUGGUGUAGCAGGUGCA	191	3441	CUCUUAUUGCAUGGACCA	1842
3441	GAGUGAUGAUUAUUAAG	192	GAGUGAUGAUUAUUAAG	192	3441	GAGUGAUGAUUAUUAAG	192	3459	CUUUAUUAUUAUACAUC	1843
3459	GUUAAUUGGCGCCUUAUA	193	GUUAAUUGGCGCCUUAUA	193	3459	GUUAAUUGGCGCCUUAUA	193	3477	UGUAAGAGGCGCAUUAAG	1844
3477	AGUAGGAGGCGUUAUUG	194	AGUAGGAGGCGUUAUUG	194	3477	AGUAGGAGGCGUUAUUG	194	3495	CAACAAGACCCUCCUACU	1845
3495	GCUUUCUGGACAUAUUCU	195	GCUUUCUGGACAUAUUCU	195	3495	GCUUUCUGGACAUAUUCU	195	3513	AAGAUUAUGUCCAGAAAGC	1846
3513	UGCUAAGAGAGUGUGCAU	196	UGCUAAGAGAGUGUGCAU	196	3513	UGCUAAGAGAGUGUGCAU	196	3531	AUGCAGACACUUCUUAACA	1847
3531	UGUUGUUGGACCUAACCUA	197	UGUUGUUGGACCUAACCUA	197	3531	UGUUGUUGGACCUAACCUA	197	3549	UAGGUUAGGUCCCAACA	1848
3549	AAUUGCAGGUGAGGACAUC	198	AAUUGCAGGUGAGGACAUC	198	3549	AAUUGCAGGUGAGGACAUC	198	3567	GAGUCCUACCCUGCAUUA	1849
3567	CCAGCUUCUUAAGGACGCA	199	CCAGCUUCUUAAGGACGCA	199	3567	CCAGCUUCUUAAGGACGCA	199	3585	UGUGCCUUAAGAAAGCUGG	1850
3585	AUAUGAAAUUAUUAUUA	200	AUAUGAAAUUAUUAUUA	200	3585	AUAUGAAAUUAUUAUUA	200	3603	UGAAUUGAAAUUAUUAUUA	1851
3603	ACAGGACAUUAUUAUUA	201	ACAGGACAUUAUUAUUA	201	3603	ACAGGACAUUAUUAUUA	201	3621	UGCAAGUAAGAUUCCUUGU	1852
3621	ACCAUUGUUGUACGAGGC	202	ACCAUUGUUGUACGAGGC	202	3621	ACCAUUGUUGUACGAGGC	202	3639	GCCUGCUGACAAUUAUGGU	1853
3639	CAUAUUUGGUGUAACCA	203	CAUAUUUGGUGUAACCA	203	3639	CAUAUUUGGUGUAACCA	203	3657	UGGUUUAAGCACCACAAUUG	1854
3657	ACUUCAGUCUUAACAAGUG	204	ACUUCAGUCUUAACAAGUG	204	3657	ACUUCAGUCUUAACAAGUG	204	3675	CACUUGUAAAGACUGAAGU	1855

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3675	GUGCGUGCAGACGGUUCGU	205	3675	GUGCGUGCAGACGGUUCGU	205	3693	ACGAACCGUCUGCAGCGAC	1856
3693	UACACAGGUUUAUUAUGCA	206	3693	UACACAGGUUUAUUAUGCA	206	3711	UGCAUAUAUAAACCGUGUA	1857
3711	AGUCAAGCAGAAAGCUCU	207	3711	AGUCAAGCAGAAAGCUCU	207	3729	AAGAGCAUUGUCUAUUGACU	1858
3729	UUAUGAGCAGGUUGUCAUG	208	3729	UUAUGAGCAGGUUGUCAUG	208	3747	CAUGACAACCCUGCUCAUAA	1859
3747	GGUAUAUCUUGAUAAACCG	209	3747	GGUAUAUCUUGAUAAACCG	209	3765	CAGGUUAUCAAGAUAAUCC	1860
3765	GGAAGCCUAGAGUGGAAGCA	210	3765	GGAAGCCUAGAGUGGAAGCA	210	3783	UGCUUCCACUCUAGGCUUC	1861
3783	ACCUAAACACAGAGGAGCCA	211	3783	ACCUAAACACAGAGGAGCCA	211	3801	UGGCUCCUCUUGUUUAGGU	1862
3801	ACCAACACACAGAAUUC	212	3801	ACCAACACACAGAAUUC	212	3819	GGAUAUUCUGUGUUUUGGU	1863
3819	CAAAACUGAGGAGAAUUC	213	3819	CAAAACUGAGGAGAAUUC	213	3837	AGAUUUUCCUCAGUUUUG	1864
3837	UGUGUACACAGAACCCUGUC	214	3837	UGUGUACACAGAACCCUGUC	214	3855	GACAGGCUUCUGUACGACA	1865
3855	CGAUGUGAAGCCAAAUUU	215	3855	CGAUGUGAAGCCAAAUUU	215	3873	AAUUUUUGGCUUCACAUCC	1866
3873	UAAGGCCUGCAUUGAUGAG	216	3873	UAAGGCCUGCAUUGAUGAG	216	3891	CUCAUAUUGCAGGCCUUA	1867
3891	GGUACACACACACUGGAA	217	3891	GGUACACACACACUGGAA	217	3909	UUCAGUGUUGUGGUAACC	1868
3909	AGAAACUAGUUUUCUACC	218	3909	AGAAACUAGUUUUCUACC	218	3927	GGUAAGAAACUUAGUUUCU	1869
3927	CAUAAGUUAUCUUGUUU	219	3927	CAUAAGUUAUCUUGUUU	219	3945	AAACAAGAGUAACUUAUUG	1870
3945	UGCUGAUUAUUAUUGGUAAG	220	3945	UGCUGAUUAUUAUUGGUAAG	220	3963	CUUACCAUUGAUUAUCAGCA	1871
3963	GCUUUAACCAUUAUUCUAG	221	3963	GCUUUAACCAUUAUUCUAG	221	3981	CUGAGAAUCAUGGUAAGC	1872
3981	GAACAUGCUUAAGGUGGAA	222	3981	GAACAUGCUUAAGGUGGAA	222	3999	UUCACCCUUAAGCAUUGUC	1873
3999	AGAUUAGUCUUUCCUUGAG	223	3999	AGAUUAGUCUUUCCUUGAG	223	4017	CUGAAGGAAAGACAUUUCU	1874
4017	GGAAGGUGCACCUCUACUG	224	4017	GGAAGGUGCACCUCUACUG	224	4035	CAUGUAAGGUGCAUCCUUC	1875
4035	GGUAGGUGAUGUUAUCACU	225	4035	GGUAGGUGAUGUUAUCACU	225	4053	AGUGUAACAUACCCUACC	1876
4053	UAGUGGUGAUUAUCACUUG	226	4053	UAGUGGUGAUUAUCACUUG	226	4071	ACAAGUGAUUACCCACUA	1877
4071	UGUUGUAUAACCCUCCAAA	227	4071	UGUUGUAUAACCCUCCAAA	227	4089	UUUGAGGGUAUUAUACACA	1878
4089	AAAGGUGGUGGCACUACU	228	4089	AAAGGUGGUGGCACUACU	228	4107	AGUAGUCCACCAGCCUUCU	1879
4107	UAGGAGUCUCUACAAGGCU	229	4107	UAGGAGUCUCUACAAGGCU	229	4125	AGCUCUUGAGAGCAUCUCA	1880
4125	UUUGAAGAAAGUGCCAGUU	230	4125	UUUGAAGAAAGUGCCAGUU	230	4143	AACUGGCACUUCUUCUCAA	1881
4143	UGAUGAGUAUAUAACCCACG	231	4143	UGAUGAGUAUAUAACCCACG	231	4161	CGUGGUUAUAUACUACA	1882
4161	GUACCCUGGACAAAGGAUGU	232	4161	GUACCCUGGACAAAGGAUGU	232	4179	ACAUCUUGUCCAGGGUAC	1883
4179	UGCUGGUUAUACACUUGAG	233	4179	UGCUGGUUAUACACUUGAG	233	4197	CUCAAGUGUAUAACAGCA	1884
4197	GGAAGCUAAGACUGCUCU	234	4197	GGAAGCUAAGACUGCUCU	234	4215	AAGAGCAGUUAAGCUUCC	1885
4215	UAAGAAUUGCAAUCUGCA	235	4215	UAAGAAUUGCAAUCUGCA	235	4233	UGCAGAUUUGCAUUCUUA	1886
4233	AUUUAUGUACUACCUUCA	236	4233	AUUUAUGUACUACCUUCA	236	4251	UGAAGGUAAGUACAUAUAAU	1887
4251	AGAAGCACCUAUUGCUAAG	237	4251	AGAAGCACCUAUUGCUAAG	237	4269	CUUAGCAUUAAGGUGCUUCU	1888
4269	GGAAGAGAUUUCUAGGAACU	238	4269	GGAAGAGAUUUCUAGGAACU	238	4287	AGUUCCUAGAAUCUUCUCC	1889
4287	UGUAUCCUGGAAUUAUGAGA	239	4287	UGUAUCCUGGAAUUAUGAGA	239	4305	UCUCAAUUCCAGGAUACA	1890
4305	AGAAUUGCUUGCUAUGCU	240	4305	AGAAUUGCUUGCUAUGCU	240	4323	AGCAUGAGCAAGCAUUCU	1891
4323	UGAAGAGACAAAGAAUUA	241	4323	UGAAGAGACAAAGAAUUA	241	4341	UAUUUUUCUUGUCUUA	1892
4341	AAUGCCUAUUAUGCAUGAU	242	4341	AAUGCCUAUUAUGCAUGAU	242	4359	AUCCAGCAUAUAGGCAU	1893
4359	UGUUAAGCCAAUUAUGGCA	243	4359	UGUUAAGCCAAUUAUGGCA	243	4377	UCCCAUUAUGGCUCAACA	1894
4377	AACCAUCCAAACUAAGUAU	244	4377	AACCAUCCAAACUAAGUAU	244	4395	AUACUUAUGGUGGUAU	1895
4395	UAAAGGAAUUAUAAUUA	245	4395	UAAAGGAAUUAUAAUUA	245	4413	UUGAAUUUAUAAUCCUUA	1896
4413	AGAGGGCAUUGUAGACUAU	246	4413	AGAGGGCAUUGUAGACUAU	246	4431	AUAGUCAACGAGGCCUUCU	1897

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4431	UGGUGCCGAAUUCUUCUUU	247	4431	UGGUGCCGAAUUCUUCUUU	247	4449	AAAGAAGAAUCGGACACCA	1898
4449	UUUACUUAAGAAAGCCU	248	4449	UUUACUUAAGAAAGCCU	248	4467	AGGCUUUUACUAGUAAA	1899
4467	UGUAGCUUUAUUAUACG	249	4467	UGUAGCUUUAUUAUACG	249	4485	CGUAAUUAAGAGCUACA	1900
4485	GAAGCUGAACUCUUAUU	250	4485	GAAGCUGAACUCUUAUU	250	4503	AUUUAGAGAGUUCAGCUUC	1901
4503	UGAGCCGCUUGACAAUUG	251	4503	UGAGCCGCUUGACAAUUG	251	4521	CAUUGUGACAAGCGGCUCA	1902
4521	GCCAAUUGGUUAUGGACA	252	4521	GCCAAUUGGUUAUGGACA	252	4539	UGUCACAUAAACCAUUGGC	1903
4539	ACAUGGUUUAUUAUGAA	253	4539	ACAUGGUUUAUUAUGAA	253	4557	UUAAGAUUAAACCAUGU	1904
4557	AGAGGCGCGCGCUUAUG	254	4557	AGAGGCGCGCGCUUAUG	254	4575	CAUACAGCGCGCAGCCUGU	1905
4575	GCGUUCUUAAGAGCCUUC	255	4575	GCGUUCUUAAGAGCCUUC	255	4593	AGGAGCUUUAAGAGAACGC	1906
4593	UGCGUAGUGUCAGUAUCA	256	4593	UGCGUAGUGUCAGUAUCA	256	4611	UGUACUGACACUACGCGCA	1907
4611	AUCACAGAUUGCUUAUCU	257	4611	AUCACAGAUUGCUUAUCU	257	4629	AGUAAACAGCAUCUGGUGAU	1908
4629	UACAUAAUUAUGUACCCU	258	4629	UACAUAAUUAUGUACCCU	258	4647	GAGGUUCCAUUAUUAUGUA	1909
4647	CACUUCGUAUCAAGACA	259	4647	CACUUCGUAUCAAGACA	259	4665	UGUCUUUGAUGACGAAUGG	1910
4665	AUCUGAGGAGCACUUAUGA	260	4665	AUCUGAGGAGCACUUAUGA	260	4683	UACAAAGUGCUCUCCAGAU	1911
4683	AGAAACAGUUUCUUUGGCU	261	4683	AGAAACAGUUUCUUUGGCU	261	4701	AGCCAAAGAAACUGUUUCU	1912
4701	UGGCUUUAACAGAGUUGG	262	4701	UGGCUUUAACAGAGUUGG	262	4719	CCAAUCUCUGUAAAGAGCCA	1913
4719	GUCCUUAUCAGGACGCGU	263	4719	GUCCUUAUCAGGACGCGU	263	4737	ACGCUUCUCCUGAAUAGGAC	1914
4737	UACAGAGUUAAGGUUUGAA	264	4737	UACAGAGUUAAGGUUUGAA	264	4755	UUAACACACUAAACUCUGUA	1915
4755	AUUUCUUAAGCGGUGGAC	265	4755	AUUUCUUAAGCGGUGGAC	265	4773	GUCACACCGCUUAAAGAAU	1916
4773	CAAAUUGUGUACCAACACU	266	4773	CAAAUUGUGUACCAACACU	266	4791	AGUGUGUACACAAUUUUG	1917
4791	UCUGGAGAGCCCGUCGAG	267	4791	UCUGGAGAGCCCGUCGAG	267	4809	CUCGACGGGCUCCUCCAGA	1918
4809	GUUUAUCUUAAGCGGUGAG	268	4809	GUUUAUCUUAAGCGGUGAG	268	4827	CUCACCGUCAAAGUAGAAAC	1919
4827	GGUUCUUAACUUAAGACAA	269	4827	GGUUCUUAACUUAAGACAA	269	4845	UUUGUCAAGUGAAAGAAC	1920
4845	ACUAAAGAGUCUUAUCC	270	4845	ACUAAAGAGUCUUAUCC	270	4863	GGUAAAGAGACUCUUUAGU	1921
4863	CCUGCGGGAGGUUAAGACU	271	4863	CCUGCGGGAGGUUAAGACU	271	4881	AGUCUUAAACUCCCGCAGG	1922
4881	UAUAAAGUGUUAACAAU	272	4881	UAUAAAGUGUUAACAAU	272	4899	AGUUGUGAACACUUUUAUA	1923
4899	UGUGGACACACUUAUCUC	273	4899	UGUGGACACACUUAUCUC	273	4917	GAGAUUAGUGUUGUCCACA	1924
4917	CCACACACAGCUUUGGUAU	274	4917	CCACACACAGCUUUGGUAU	274	4935	AUCCACAAGCUGUGUGG	1925
4935	UAUGUCUAUGACAUUUGGA	275	4935	UAUGUCUAUGACAUUUGGA	275	4953	UCCAUAUGUCAUAGACAU	1926
4953	ACAGCAGUUUGGUCCAACA	276	4953	ACAGCAGUUUGGUCCAACA	276	4971	UGUUGGACCAACUUGUGU	1927
4971	AUACUUGGAUGGUGUGUAU	277	4971	AUACUUGGAUGGUGUGUAU	277	4989	AUCAGCACAUCCAAGUAU	1928
4989	UGUUAACAAAUUAACCCU	278	4989	UGUUAACAAAUUAACCCU	278	5007	AGGUUUAUUAUUAUUAACA	1929
5007	UAUGUUAUUAUUAUUAACA	279	5007	UAUGUUAUUAUUAUUAACA	279	5025	ACCCUCAUAUUUAUUAACA	1930
5025	UAAGACUUAUUAUUAUUA	280	5025	UAAGACUUAUUAUUAUUA	280	5043	UAGUUAUUAUUAUUAUUA	1931
5043	ACCUAGUGAUGACACACUA	281	5043	ACCUAGUGAUGACACACUA	281	5061	UAGUGUGUCAUACUAGGU	1932
5061	ACGUAGUGAAGCUUUGGAG	282	5061	ACGUAGUGAAGCUUUGGAG	282	5079	CUGGAAAGCUUACUACUGU	1933
5079	GUACUACCAUACUUAUUA	283	5079	GUACUACCAUACUUAUUA	283	5097	AUCAAGAGUAUGGUAGUAC	1934
5097	UGAGAGUUAUUAUUAUUA	284	5097	UGAGAGUUAUUAUUAUUA	284	5115	CCUACCAAGAAACUCUCA	1935
5115	GUACAGUUAUUAUUAUUA	285	5115	GUACAGUUAUUAUUAUUA	285	5133	GUUUAAGCAGACAUUUAAC	1936
5133	CCACACAAAGAAUUGGAAA	286	5133	CCACACAAAGAAUUGGAAA	286	5151	UUUCCAUUUUUUUGUGUGG	1937
5151	AUUUCCUUAAGUUGGUGU	287	5151	AUUUCCUUAAGUUGGUGU	287	5169	ACCACCAACUUGAGGAAU	1938
5169	UUUAAACUUAUUAUUAUUGG	288	5169	UUUAAACUUAUUAUUAUUGG	288	5187	CCAUUUUAUUAUUAUUAU	1939

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5187	GGCUGAUAAACAAUUGUUAU	289	5187	GGCUGAUAAACAAUUGUUAU	289	5205	AUAACAAUUGUUAUCAGCC	1940
5205	UUUGUCUAGUGUUUUUAUA	290	5205	UUUGUCUAGUGUUUUUAUA	290	5223	UAUAACAAACUAGACAAA	1941
5223	AGCACUUAACAGCUUGAA	291	5223	AGCACUUAACAGCUUGAA	291	5241	UUGAAGCUGUUGAAGGCU	1942
5241	AGUCAAUUAAGUACCA	292	5241	AGUCAAUUAAGUACCA	292	5259	UGGUGAUUGAAUUUGCU	1943
5259	AGCACUUAAGAGGCUUAU	293	5259	AGCACUUAAGAGGCUUAU	293	5277	AUAAGCCUUGAAGGCU	1944
5277	UUAUAGAGCCGUGUGU	294	5277	UUAUAGAGCCGUGUGU	294	5295	ACCAGCAGGCGUCUAUA	1945
5295	UGAUGCUGCUAACUUGU	295	5295	UGAUGCUGCUAACUUGU	295	5313	ACAAAGUUAAGACAUUA	1946
5313	UGCACUUAACUCGCUAC	296	5313	UGCACUUAACUCGCUAC	296	5331	GUAAAGCAGUAGAGUGCA	1947
5331	CAGUAAUAAACUGUUGG	297	5331	CAGUAAUAAACUGUUGG	297	5349	GCCAACAGUUUUUAUACUG	1948
5349	CGAGCUUGGUGAGUCAGA	298	5349	CGAGCUUGGUGAGUCAGA	298	5367	UCUGACAUCCACCAAGCUG	1949
5367	AGAAACUAGACCAUCUU	299	5367	AGAAACUAGACCAUCUU	299	5385	AAGAUGGUCUAGUUUCU	1950
5385	UCUACAGCAUGCUAAUUG	300	5385	UCUACAGCAUGCUAAUUG	300	5403	CAAAUJAGCAUGGUGUAGA	1951
5403	GGAAUCUGCAAAGCGAGUU	301	5403	GGAAUCUGCAAAGCGAGUU	301	5421	AACUCGUUUUGCAGAUCC	1952
5421	UCUUAUUGUGUGUGUAAA	302	5421	UCUUAUUGUGUGUGUAAA	302	5439	UUUACACACCAUUAAGA	1953
5439	ACAUUGUGGUCAGAAACU	303	5439	ACAUUGUGGUCAGAAACU	303	5457	AGUUUUUGUGACCAUUGU	1954
5457	UACUACCUUAACGGGUGUA	304	5457	UACUACCUUAACGGGUGUA	304	5475	UACACCCGUUAAGGUGUA	1955
5475	AGAAGCUGUGAUUAUUG	305	5475	AGAAGCUGUGAUUAUUG	305	5493	CAUAUACUACACAGCUUCU	1956
5493	GGGUACUCUUAUUAUGAU	306	5493	GGGUACUCUUAUUAUGAU	306	5511	AUCAUAAGAUAGAGUACCC	1957
5511	UAUUCUUAAGACAGGUGUU	307	5511	UAUUCUUAAGACAGGUGUU	307	5529	AACACCUUGUCUUAAGAUUA	1958
5529	UUCUUAUCCAUUGUGUGU	308	5529	UUCUUAUCCAUUGUGUGU	308	5547	ACACACAUUGGAAUGGAA	1959
5547	UGGUGUGUAGUACACAA	309	5547	UGGUGUGUAGUACACAA	309	5565	UUGUGUAGCAUCACGACCA	1960
5565	AUAUCUAGUACAAAGAG	310	5565	AUAUCUAGUACAAAGAG	310	5583	CUCUUGUUGUACUAGAUU	1961
5583	GUCUUCUUAUUGUUAUG	311	5583	GUCUUCUUAUUGUUAUG	311	5601	CAUCAUACAAAGAGAC	1962
5601	GUCUGCACCCUGUGUGAG	312	5601	GUCUGCACCCUGUGUGAG	312	5619	CUCAGCAGGUGGUGCAGAC	1963
5619	GUUAAUUAACAGCAAGGU	313	5619	GUUAAUUAACAGCAAGGU	313	5637	ACCUUGCUGUUAUUUAUAC	1964
5637	UACAUUCUUAUGUGCGAAU	314	5637	UACAUUCUUAUGUGCGAAU	314	5655	AUUCGCACAUAAAGAUUA	1965
5655	UGAGUACACUGGUUAUUAU	315	5655	UGAGUACACUGGUUAUUAU	315	5673	UAUUAUACCAUGUUAUUAU	1966
5673	UCAGUGUGGUCUUAUUAU	316	5673	UCAGUGUGGUCUUAUUAU	316	5691	AGUGUUAUAGCACCACUGA	1967
5691	UCAUUAUACUGCUAAGGAG	317	5691	UCAUUAUACUGCUAAGGAG	317	5709	CUCUUAAGCAGUUAUUAUGA	1968
5709	GACCCUUAUCGUUAUUGAC	318	5709	GACCCUUAUCGUUAUUGAC	318	5727	GUCAAUACGAUAGAGGUG	1969
5727	CGGAGCUCACCUUAACAAAG	319	5727	CGGAGCUCACCUUAACAAAG	319	5745	CUUUUAAGGUGAGCUCUG	1970
5745	GAUGUCAGAGUACAAAGGA	320	5745	GAUGUCAGAGUACAAAGGA	320	5763	UCCUUAUACUCUGACAU	1971
5763	ACCAGUGACUGAUUUUUC	321	5763	ACCAGUGACUGAUUUUUC	321	5781	GAUUAUACAGUACUCUGU	1972
5781	CUACAAGGAACAUUUAU	322	5781	CUACAAGGAACAUUUAU	322	5799	GUAAAGUUAUCCUUGUAG	1973
5799	CACUACAACCAUUAAGCCU	323	5799	CACUACAACCAUUAAGCCU	323	5817	AGGCUUUGUUGUUGUAGUG	1974
5817	UGUGUGUUAUUAUUAUUAU	324	5817	UGUGUGUUAUUAUUAUUAU	324	5835	AUCGAGUUUAUACGACACA	1975
5835	UGGAGUUAUUAUUAUUAU	325	5835	UGGAGUUAUUAUUAUUAU	325	5853	CUCUGUGUUAUUAUUAU	1976
5853	GAUUGAACCAUUAUUAUUAU	326	5853	GAUUGAACCAUUAUUAUUAU	326	5871	AUCCAAUUAUUAUUAUUAU	1977
5871	UUAUUAUUAUUAUUAUUAU	327	5871	UUAUUAUUAUUAUUAUUAU	327	5889	AUCCUUAUUAUUAUUAUUAU	1978
5889	UUAUUAUUAUUAUUAUUAU	328	5889	UUAUUAUUAUUAUUAUUAU	328	5907	CUCUGUUAUUAUUAUUAUUAU	1979
5907	GCAGCCUUAUUAUUAUUAU	329	5907	GCAGCCUUAUUAUUAUUAU	329	5925	UACAAGGUCUUAUUAUUAUUAU	1980
5925	ACCAACUUAUUAUUAUUAU	330	5925	ACCAACUUAUUAUUAUUAU	330	5943	UGGUUAUUAUUAUUAUUAUUAU	1981

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5943	AAAUGCGAGUUUUUGAUAAU	331	5943	AAUUGCGAGUUUUUGAUAAU	331	5961	AUUUAUCAAACUUGCAUUU	1982
5961	UUUUAACACUCACUAGUUCU	332	5961	UUUUAACACUCACUAGUUCU	332	5979	AGAAACUAGUGUUUGAAU	1983
5979	UUAACACAAAUUUGCUGAU	333	5979	UUAACACAAAUUUGCUGAU	333	5997	AUCAGCAAUUUUGUGUUA	1984
5997	UGAUUUAAAUCAAUAGACA	334	5997	UGAUUUAAAUCAAUAGACA	334	6015	UGUCAUUUGAUUUAAAUCA	1985
6015	AGGCUUACAAAGCCAGCU	335	6015	AGGCUUACAAAGCCAGCU	335	6033	AGUGGCUUUUGUGAAGCCU	1986
6033	UUCACGAGAGCAUUCUGUC	336	6033	UUCACGAGAGCAUUCUGUC	336	6051	GACAGUAGCUCUCUGGAA	1987
6051	CACAUUCUCCAGCUUUG	337	6051	CACAUUCUCCAGCUUUG	337	6069	CAAGUCUGGGAAGAUUG	1988
6069	GAAUGGCGAGUAGUGGCU	338	6069	GAAUGGCGAGUAGUGGCU	338	6087	AGCACUACUAGCGCAUUC	1989
6087	UAUUGACUAUAGACACUAU	339	6087	UAUUGACUAUAGACACUAU	339	6105	AUAGUGUCUAUAGUCAUA	1990
6105	UUCAGCGAGUUUCAAAGAA	340	6105	UUCAGCGAGUUUCAAAGAA	340	6123	UUUCUUGAAACUUGCGUAA	1991
6123	AGGUGUAUUUAGUGCAU	341	6123	AGGUGUAUUUAGUGCAU	341	6141	AUGGAGUAUUUAGGCCUUA	1992
6141	UAAGCCAAUUGUUGGCAC	342	6141	UAAGCCAAUUGUUGGCAC	342	6159	GUGCAAACAAUUGGCUUA	1993
6159	CAUUAAACGAGGUAACACC	343	6159	CAUUAAACGAGGUAACACC	343	6177	GGUUGUAGCCUGGUUAAUG	1994
6177	CAAGACAACGUUCAAACCA	344	6177	CAAGACAACGUUCAAACCA	344	6195	UGGUUUGAACGUUGUCUUG	1995
6195	AAACACUUGGUGUUUACGU	345	6195	AAACACUUGGUGUUUACGU	345	6213	ACGUAAACACCAAGUGUUU	1996
6213	UUUGUUUUGGAGUACAAAG	346	6213	UUUGUUUUGGAGUACAAAG	346	6231	CUUUGUACUCCAAAGACAA	1997
6231	GCCAGUAGAUUUAUCAAU	347	6231	GCCAGUAGAUUUAUCAAU	347	6249	AUUUGAAGUAUCUACUGGC	1998
6249	UUCAUUUGAAGUUCUGGCA	348	6249	UUCAUUUGAAGUUCUGGCA	348	6267	UGCCAGAAAUUCAAAGAA	1999
6267	AGUAGAAGACACACAAGGA	349	6267	AGUAGAAGACACACAAGGA	349	6285	UCCUUGUGUGUUCUUAU	2000
6285	AUUGGACAAUUCUUGUUG	350	6285	AUUGGACAAUUCUUGUUG	350	6303	ACAAGCAAGUUGUCCAUU	2001
6303	UGAAAGUACAAACCCACC	351	6303	UGAAAGUACAAACCCACC	351	6321	GGUGGUUGUUGACUUAU	2002
6321	CUCUGAAGAGUAGUGGAA	352	6321	CUCUGAAGAGUAGUGGAA	352	6339	UUCACUACUUCUUCAGAG	2003
6339	AAUUCUACCAUACAGAG	353	6339	AAUUCUACCAUACAGAG	353	6357	CUUCUGUAGUGUAGGAUU	2004
6357	GGAAGUCAUAGUGUGAC	354	6357	GGAAGUCAUAGUGUGAC	354	6375	GUCACACUCUAGACUUC	2005
6375	CGUGAAACUACCGAAGUU	355	6375	CGUGAAACUACCGAAGUU	355	6393	AACUUGGUGUUGUUCACG	2006
6393	UGUAGGCAUUGUUAUUAU	356	6393	UGUAGGCAUUGUUAUUAU	356	6411	AAGUAGACAUUGGCUACA	2007
6411	UAAACCAUACAGUAGAGGU	357	6411	UAAACCAUACAGUAGAGGU	357	6429	ACCUUACUUGUAGGUUUA	2008
6429	UGUUAAGUAACACAAGAG	358	6429	UGUUAAGUAACACAAGAG	358	6447	CUCUUGUGUUAUUAACA	2009
6447	GUUAGGUCAUAGAGAUUU	359	6447	GUUAGGUCAUAGAGAUUU	359	6465	AAGUCCUACUAGCCUAA	2010
6465	UAUGGCGUUAUUGUGGAA	360	6465	UAUGGCGUUAUUGUGGAA	360	6483	UUCACAUAAAGCAGCAUA	2011
6483	AAACACAAGCAUUAUUAU	361	6483	AAACACAAGCAUUAUUAU	361	6501	AUUGGUAUUGUUGUUAU	2012
6501	UAAGAAACCUAAGGCUU	362	6501	UAAGAAACCUAAGGCUU	362	6519	AAGCUAUAGGUUUCUUA	2013
6519	UUCACUAGCCUUAUUAU	363	6519	UUCACUAGCCUUAUUAU	363	6537	UAAACCUAAGGCUAGUUA	2014
6537	AAAAACAUIUGCCACUUAU	364	6537	AAAAACAUIUGCCACUUAU	364	6555	AUGAGUGGCAUUGUUAU	2015
6555	UGGUUUUGGCUUAUUAU	365	6555	UGGUUUUGGCUUAUUAU	365	6573	AUUAUUUGCAGCAUUAU	2016
6573	UAGUUGUCCUUGGAGUAA	366	6573	UAGUUGUCCUUGGAGUAA	366	6591	UUUACUCCAAAGGAACUA	2017
6591	AAUUUUGGCUUAUUAU	367	6591	AAUUUUGGCUUAUUAU	367	6609	UUUGACAUAAAGCAAAU	2018
6609	ACCAUUCUUAAGGACAAGCA	368	6609	ACCAUUCUUAAGGACAAGCA	368	6627	UGUUGUCCUUAAGAAUGGU	2019
6627	AGCAUUUAACAUAUUAU	369	6627	AGCAUUUAACAUAUUAU	369	6645	AUUUGUUGUUAUUAU	2020
6645	UUGGCUUAAGAGAUUAAGCA	370	6645	UUGGCUUAAGAGAUUAAGCA	370	6663	UGCUAAUCUUAAGCGCAA	2021
6663	ACAACGUGUGUUAUUAU	371	6663	ACAACGUGUGUUAUUAU	371	6681	AUUGUUAACACACGUGU	2022
6681	UUUAUAGCCUUAUUGUUAU	372	6681	UUUAUAGCCUUAUUGUUAU	372	6699	AAACACAUAAAGGCAUUA	2023

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6699	UACAUUAUUGUCCAAUUG	373	6699	UACAUUAUUGUCCAAUUG	373	6717	CAAUUGGAACAUAUAUGUA	2024
6717	GUGUACUUUUUACUAAAAGU	374	6717	GUGUACUUUUUACUAAAAGU	374	6735	ACUUUUUAGUAAAAGUACAC	2025
6735	UACCAUUCUUAAGAAUUA	375	6735	UACCAUUCUUAAGAAUUA	375	6753	UCUUAUUCUAGAAUUGGUA	2026
6753	AGCUUCACUACUACUACU	376	6753	AGCUUCACUACUACUACU	376	6771	AGUUGUAGGUAGUGAAGCU	2027
6771	UAUUGCUAAAAUAGUGUU	377	6771	UAUUGCUAAAAUAGUGUU	377	6789	AACACUUAUUAUAGCAUA	2028
6789	UAGAGUGUUGCUAAUUA	378	6789	UAGAGUGUUGCUAAUUA	378	6807	UAUUUUAGCAACACUCUUA	2029
6807	AUGUUUGGAGCCGGCAU	379	6807	AUGUUUGGAGCCGGCAU	379	6825	AAUGCCGGCAUCCAAACUA	2030
6825	UAUUUUGGAGGACACCC	380	6825	UAUUUUGGAGGACACCC	380	6843	GGGUGACUUCACAUAAUUA	2031
6843	CAAAUUUCUAAAUUGUUC	381	6843	CAAAUUUCUAAAUUGUUC	381	6861	GAAACUUUJAGAAAUUUG	2032
6861	CACAAUCGCUAUGGCUA	382	6861	CACAAUCGCUAUGGCUA	382	6879	UAGCCACAUAGCGAUUGUG	2033
6879	AUUGUUGUUAAGUUAUUGC	383	6879	AUUGUUGUUAAGUUAUUGC	383	6897	GCAAAUCUUAACAAACUA	2034
6897	CUUAGGUUCUUAUUCUG	384	6897	CUUAGGUUCUUAUUCUG	384	6915	ACAGAUUAGAGAACCUAAG	2035
6915	UGAACUGCGCUUUUGGU	385	6915	UGAACUGCGCUUUUGGU	385	6933	ACCAAAAGCAGCAGUUA	2036
6933	UGUACUCUUAUCUAAUUA	386	6933	UGUACUCUUAUCUAAUUA	386	6951	AAAUUJAGAUAGAGUACA	2037
6951	UGUGUCUCCUUCUUAUUGU	387	6951	UGUGUCUCCUUCUUAUUGU	387	6969	ACAAUUAAGAGGAGCACCA	2038
6969	UAUUGGCUUAAGAAUUG	388	6969	UAUUGGCUUAAGAAUUG	388	6987	CAAUUCUCUACGCCAUUA	2039
6987	GUACUUAUUAUGGUAAC	389	6987	GUACUUAUUAUGGUAAC	389	7005	GUUAGAGCAUUAAGAUAC	2040
7005	CGUUAUUAUGGAAUUC	390	7005	CGUUAUUAUGGAAUUC	390	7023	GAAUCCAUUAGUUAACG	2041
7023	CUGGAGGUUCUUAUUCU	391	7023	CUGGAGGUUCUUAUUCU	391	7041	AGGAAAGAACCUUCACAG	2042
7041	UUGCAGCAUUAUUAAGU	392	7041	UUGCAGCAUUAUUAAGU	392	7059	ACUUAACAAUUGCUGCAA	2043
7059	UGGAUUAAGACUCCUUAU	393	7059	UGGAUUAAGACUCCUUAU	393	7077	UAUAGGGAGUUAUUAUCCA	2044
7077	UUCUUAUCCAGCUUUGAA	394	7077	UUCUUAUCCAGCUUUGAA	394	7095	UUAAGAGCUGGUAUAGAA	2045
7095	AACCAUUCAGGACGAU	395	7095	AACCAUUCAGGACGAU	395	7113	AAUCGUCACCUAAUUGGU	2046
7113	UUAUCGUAACAGCUAGAC	396	7113	UUAUCGUAACAGCUAGAC	396	7131	GUCUAGCUUUAUAGGAU	2047
7131	CUUGACAUAUUAAGGUCUG	397	7131	CUUGACAUAUUAAGGUCUG	397	7149	CAGACCUAAAUUUGUCAAG	2048
7149	GGCCGCGAGUGGGUUAUUG	398	7149	GGCCGCGAGUGGGUUAUUG	398	7167	CAAAACCCACUCACGCGCC	2049
7167	GGCAUAUAUUGUUGACA	399	7167	GGCAUAUAUUGUUGACA	399	7185	UGUGAACAAUUAUUAUGCC	2050
7185	AAAUUUCUUUAUUAUUA	400	7185	AAAUUUCUUUAUUAUUA	400	7203	UAUUAUUAUUAUUAUUA	2051
7203	AGGCUUUCAGCUUAUUAUG	401	7203	AGGCUUUCAGCUUAUUAUG	401	7221	CAUUAUAGCUUUAUUAUUA	2052
7221	GCAGGUGUUCUUGGCUAU	402	7221	GCAGGUGUUCUUGGCUAU	402	7239	UAUAGCCAAAGAACACCUUGC	2053
7239	UUUUGCUAGCUUAUUAUC	403	7239	UUUUGCUAGCUUAUUAUC	403	7257	GAUUAUUAUUAUUAUUA	2054
7257	CAGCAUUCUUGGCUAUG	404	7257	CAGCAUUCUUGGCUAUG	404	7275	CAUGAGCCAAAGAAUUGCUG	2055
7275	GUGGUUAUUAUUAUUAUUA	405	7275	GUGGUUAUUAUUAUUAUUA	405	7293	AAUACUUAUUAUUAUUA	2056
7293	UGUACAAUUGGACCCGUU	406	7293	UGUACAAUUGGACCCGUU	406	7311	AACGGGUGCCAUUUAUUA	2057
7311	UUCUGCAUUGGUUAGGAUG	407	7311	UUCUGCAUUGGUUAGGAUG	407	7329	CAUCCUAAACCAUUAUUA	2058
7329	GUACAUUCUUAUUGCUUUC	408	7329	GUACAUUCUUAUUGCUUUC	408	7347	AGAAGCAAAGAAUUAUUA	2059
7347	UUUUAUUAUUAUUAUUA	409	7347	UUUUAUUAUUAUUAUUA	409	7365	CUUCCAUUAUUAUUAUUA	2060
7365	GAGCAUUGUUAUUAUUAUUA	410	7365	GAGCAUUGUUAUUAUUAUUA	410	7383	CAUGAUUAUUAUUAUUA	2061
7383	GGUUGUUGGACCUUUAUUA	411	7383	GGUUGUUGGACCUUUAUUA	411	7401	CGAAGAGGUGCAUUAUUA	2062
7401	GACUUGCAUUAUUAUUAUUA	412	7401	GACUUGCAUUAUUAUUAUUA	412	7419	UAAGCACAUAUUAUUAUUA	2063
7419	UAAGCGCAUUAUUAUUAUUA	413	7419	UAAGCGCAUUAUUAUUAUUA	413	7437	UGUGGACCAUUAUUAUUA	2064
7437	ACGCGUUAUUAUUAUUAUUA	414	7437	ACGCGUUAUUAUUAUUAUUA	414	7455	AGUUGUUAUUAUUAUUA	2065

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7455	UAUUGUUAUUGGCAUGAAG	415	7455	UAUUGUUAUUGGCAUGAAG	415	7473	CUUACAUGCCAUUAACAUA	2066
7473	GAGAUUUUUAUUGUUAU	416	7473	GAGAUUUUUAUUGUUAU	416	7491	AUAGCAUAGAAAGAUUCU	2067
7491	UGCAAUUGGAGGCGUGGC	417	7491	UGCAAUUGGAGGCGUGGC	417	7509	GCCACGGCCUCCAUUUGCA	2068
7509	CUUCUGCAAGACUCACAAU	418	7509	CUUCUGCAAGACUCACAAU	418	7527	AUUGAGUCUUGCGAGAAG	2069
7527	UUGGAAUUGUCUCAAUUGU	419	7527	UUGGAAUUGUCUCAAUUGU	419	7545	ACAAUUGAGACAUAUCCAA	2070
7545	UGACAAUUGUCACUGGU	420	7545	UGACAAUUGUCACUGGU	420	7563	ACCAGUGCAAAUUGUGUCA	2071
7563	UAGUACAUUAUUGUGAU	421	7563	UAGUACAUUAUUGUGAU	421	7581	AUCACUAUAAUUGUACUA	2072
7581	UGAAGUUGUCUGUUAUUG	422	7581	UGAAGUUGUCUGUUAUUG	422	7599	CAAUACAGGAGCAUUAUA	2073
7599	GUCACUCCAGUUAUUAAGA	423	7599	GUCACUCCAGUUAUUAAGA	423	7617	UCUUAUAAACUGGAGUAC	2074
7617	ACCAUACACCCUACUGAC	424	7617	ACCAUACACCCUACUGAC	424	7635	GUCAGUAGGUGUUAUUGU	2075
7635	CCAGUCAUGUUAUUAUUGU	425	7635	CCAGUCAUGUUAUUAUUGU	425	7653	AACAUAUACGAUGAGUGG	2076
7653	UGAUAGUUGUCUGUGAAA	426	7653	UGAUAGUUGUCUGUGAAA	426	7671	UUUCACAGCAACACUAUA	2077
7671	AAUUGGCGCUUACCCUC	427	7671	AAUUGGCGCUUACCCUC	427	7689	GAGGUGAAGCGCGCAUUAU	2078
7689	CUACUUGAGCAAGGUGGU	428	7689	CUACUUGAGCAAGGUGGU	428	7707	ACCAGCCUUGUCAAGUAG	2079
7707	UCAAAAGACCUAUGAGAGA	429	7707	UCAAAAGACCUAUGAGAGA	429	7725	UCUCUCAUAGGUCUUUUGA	2080
7725	CAUCCGCUUCCAUUUU	430	7725	CAUCCGCUUCCAUUUU	430	7743	AAAUUGGAGAGCGGAUGU	2081
7743	UGUCAUUAUAGCAAUUUG	431	7743	UGUCAUUAUAGCAAUUUG	431	7761	CAAAUUGUCUAAUUAUGA	2082
7761	GAGAGCUAACACACUAAA	432	7761	GAGAGCUAACACACUAAA	432	7779	UUUAGUGUUGUUAUAGCUC	2083
7779	AGGUUCACUGCCUUAUUAU	433	7779	AGGUUCACUGCCUUAUUAU	433	7797	AUUAUAGGAGGAGUAAUUA	2084
7797	UGUCAUUAUUAUUAUUGG	434	7797	UGUCAUUAUUAUUAUUGG	434	7815	GCCAUCAAAAUUAUUAUGA	2085
7815	CAAGUCCAAUUGCGACGAG	435	7815	CAAGUCCAAUUGCGACGAG	435	7833	CUCGUGCAUUAUUGGACUUG	2086
7833	GUCUGCUUUAAGUCUGCU	436	7833	GUCUGCUUUAAGUCUGCU	436	7851	AGCAGACUUAAGAGCAGAC	2087
7851	UUCUGUGUACUACAGUCAG	437	7851	UUCUGUGUACUACAGUCAG	437	7869	CUGACUGUAGUACACAGAA	2088
7869	GCUGAUGUGCCACCCUUAU	438	7869	GCUGAUGUGCCACCCUUAU	438	7887	AUAAGGUUGGCAUUAUAGC	2089
7887	UCUGUUGCUUAGCCAAAGCU	439	7887	UCUGUUGCUUAGCCAAAGCU	439	7905	AGCUUGGUCAAGCAACAGA	2090
7905	UCUUGUAUACAGACGUUGGA	440	7905	UCUUGUAUACAGACGUUGGA	440	7923	UCCACGUCUGAUUAACAAG	2091
7923	AGUAUAGUACUGAAGUUAUCC	441	7923	AGUAUAGUACUGAAGUUAUCC	441	7941	GGAACUUAUAGUACUUAU	2092
7941	CGUUAAGAUUUUAUUAUUG	442	7941	CGUUAAGAUUUUAUUAUUG	442	7959	AGCAUCAAACAUUAUUAACG	2093
7959	UUUAGUCGACACCCUUAUUA	443	7959	UUUAGUCGACACCCUUAUUA	443	7977	UGAAAAGGUGUCGACAUAA	2094
7977	AGCAACUUAUUAUUAUUAUCC	444	7977	AGCAACUUAUUAUUAUUAUCC	444	7995	AGGAACACUAAAAGUUGCU	2095
7995	UAUGGAAAACUUAUUAAGGCA	445	7995	UAUGGAAAACUUAUUAAGGCA	445	8013	UGCCUUAAGUUUUUUAUUA	2096
8013	ACUUGUUGCUACAGCUCAC	446	8013	ACUUGUUGCUACAGCUCAC	446	8031	GUGAGCUGUUAAGCAACAAGU	2097
8031	CAGCGAGUUAAGCAAGGUGU	447	8031	CAGCGAGUUAAGCAAGGUGU	447	8049	ACCCUUGCUUAACUUGCUG	2098
8049	UGUAGCUUUUAAGUUGGUGUC	448	8049	UGUAGCUUUUAAGUUGGUGUC	448	8067	GACACCAUUAAGGAGUACA	2099
8067	CCUUCUUAUUAUUAUUAUUA	449	8067	CCUUCUUAUUAUUAUUAUUA	449	8085	UGACACGAUUAAGAAAGG	2100
8085	AGCUGCCCGCAAGGUGU	450	8085	AGCUGCCCGCAAGGUGU	450	8103	AACACCUUGUCGGGAGCU	2101
8103	UGUUGAUACCGAUUUAUUA	451	8103	UGUUGAUACCGAUUUAUUA	451	8121	GUAACAUCGUAUUAACA	2102
8121	CACAAGGAUGUUAUUAUUA	452	8121	CACAAGGAUGUUAUUAUUA	452	8139	UUCAUAUUAUUAUUAUUA	2103
8139	AUGUCUUAUUAUUAUUAUUA	453	8139	AUGUCUUAUUAUUAUUAUUA	453	8157	AUGUAAAGUUAUUAUUA	2104
8157	UCACUCUGACUUAUUAUUA	454	8157	UCACUCUGACUUAUUAUUA	454	8175	CACUUCUUAAGUACAGUGA	2105
8175	GACAGGUGACAGUUAUUAAC	455	8175	GACAGGUGACAGUUAUUAAC	455	8193	GUUACAACUUGUACUUGUC	2106
8193	CAAUUUAUUAUUAUUAUUA	456	8193	CAAUUUAUUAUUAUUAUUA	456	8211	AUAGGUGAGCAUGAAUUAU	2107

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8211	UAAUAGGUUGAAACAUG	457	8211	UAAUAGGUUGAAACAUG	457	8229	CAUGUUUUAACCUUUAUA	2108
8229	GACGCCAGAGACUUGGC	458	8229	GACGCCAGAGACUUGGC	458	8247	GCAAGACUCUGGGCGUC	2109
8247	CGCAUGUUAUGACUUAU	459	8247	CGCAUGUUAUGACUUAU	459	8265	AUUAAGUCACUACAGCG	2110
8265	UGCAAGGCAUAUCAUAGCC	460	8265	UGCAAGGCAUAUCAUAGCC	460	8283	GGCAUUGAUUAGCCUUGCA	2111
8283	CCAAGUAGCAAAAGUCAC	461	8283	CCAAGUAGCAAAAGUCAC	461	8301	GUGACUUUUGCUACUUGG	2112
8301	CAUUGUUUCACUACUUGG	462	8301	CAUUGUUUCACUACUUGG	462	8319	CCAGUAGAGUAAACAUUG	2113
8319	GAUUGUAAAAGACUACAUG	463	8319	GAUUGUAAAAGACUACAUG	463	8337	CAUGUAGUCUUUAACAUC	2114
8337	GUCUUUAUCUGAACAGCUG	464	8337	GUCUUUAUCUGAACAGCUG	464	8355	CAGCUGUUCAGUAAAGAC	2115
8355	GCGUAAACAUAUUGUAGU	465	8355	GCGUAAACAUAUUGUAGU	465	8373	ACUACGAAUUGUUUACGC	2116
8373	UGCUGCCAAGAGAACAC	466	8373	UGCUGCCAAGAGAACAC	466	8391	GUUGUUCUUCUUGGCAGCA	2117
8391	CAUACCUUUUAGACUAACU	467	8391	CAUACCUUUUAGACUAACU	467	8409	AGUAGUCUAAAAGGUUAG	2118
8409	UUGUGCUACAAGACAGAC	468	8409	UUGUGCUACAAGACAGAC	468	8427	GUGUAGUUGUAGGACAA	2119
8427	GGUUGUCAAUGUCAUAACU	469	8427	GGUUGUCAAUGUCAUAACU	469	8445	AGUUUAGACAUUAGACAAC	2120
8445	UACUAAAUCACUCUACAG	470	8445	UACUAAAUCACUCUACAG	470	8463	CUUGAGUGAGAUUUUAGUA	2121
8463	GGUGUGUAGAUUUGUAGU	471	8463	GGUGUGUAGAUUUGUAGU	471	8481	ACUAAACAUUUAACCAACC	2122
8481	UACUUGUUUUAACUUAUG	472	8481	UACUUGUUUUAACUUAUG	472	8499	CAUAAUUAUUAACAAGUA	2123
8499	GCUUUAGGCCACAUUAUG	473	8499	GCUUUAGGCCACAUUAUG	473	8517	CAUAAUUGUGCCUUAAGC	2124
8517	GUGGUGUUCUGCGCAUUG	474	8517	GUGGUGUUCUGCGCAUUG	474	8535	CAUUGCAGCAAGAACGCAC	2125
8535	GGUUUGUUAUUGUUAUG	475	8535	GGUUUGUUAUUGUUAUG	475	8553	CAUAAAGUUAACAACAACC	2126
8553	GCCAGUACAUAUUGUCA	476	8553	GCCAGUACAUAUUGUCA	476	8571	UGACAAUUAUUGUACUGGC	2127
8571	AAUCCAUGAGUUAACACA	477	8571	AAUCCAUGAGUUAACACA	477	8589	UGUGAACCAUUGGUAU	2128
8589	AAUAGAAUAUUGGUUAC	478	8589	AAUAGAAUAUUGGUUAC	478	8607	GUAAACCAUUGUUUUAU	2129
8607	CAAAGCCAUUACAGGAGGU	479	8607	CAAAGCCAUUACAGGAGGU	479	8625	ACCAUCCUGAAUGGCUUUG	2130
8625	UUCACUCUGGACAUUAU	480	8625	UUCACUCUGGACAUUAU	480	8643	AAUGAUGUCACGAGUGACA	2131
8643	UUCUACUGAUGAUUUGUU	481	8643	UUCUACUGAUGAUUUGUU	481	8661	AAACAUAUACAGUAGAA	2132
8661	UGCAAAUAAACAUGCUGGU	482	8661	UGCAAAUAAACAUGCUGGU	482	8679	ACCAGCAUGUUUAUUGCA	2133
8679	UUUUGACGCAUGGUUUAAGC	483	8679	UUUUGACGCAUGGUUUAAGC	483	8697	GUAAACCAUGCGGUA	2134
8697	CCAGCGUGGUGGUUAUAC	484	8697	CCAGCGUGGUGGUUAUAC	484	8715	GUUAGAACCAACGCGUGG	2135
8715	CAAAUAGCAAAAGCUGC	485	8715	CAAAUAGCAAAAGCUGC	485	8733	GCAGCUUUUGUUAUUUUG	2136
8733	CCUGUAGUAGCUGCUAUC	486	8733	CCUGUAGUAGCUGCUAUC	486	8751	GAUAGCAGCUACUACAGG	2137
8751	CAUUAACAAGAGAUUGGU	487	8751	CAUUAACAAGAGAUUGGU	487	8769	ACCAUUCUCUUGUUAUUG	2138
8769	UUUCAUAGUGCCUGGCUUA	488	8769	UUUCAUAGUGCCUGGCUUA	488	8787	UAAGCCAGGCACUAGAAA	2139
8787	ACCGGUACUGUGUGAGAGA	489	8787	ACCGGUACUGUGUGAGAGA	489	8805	UCUCAGCACAGUACCCGGU	2140
8805	AGCAUACAUGGUGACUUC	490	8805	AGCAUACAUGGUGACUUC	490	8823	GAAGUCACCAUUGAUUGCU	2141
8823	CUUGCAUUUUCUACCCUGU	491	8823	CUUGCAUUUUCUACCCUGU	491	8841	ACGAGGUAGAAAUGCAAG	2142
8841	UGUUUUUAGUGCUGUUGGC	492	8841	UGUUUUUAGUGCUGUUGGC	492	8859	GCCAACAGCACUAAAACA	2143
8859	CAACAUAUUGCUACACACCU	493	8859	CAACAUAUUGCUACACACCU	493	8877	AGGUGUGUAGCAAUUGUUG	2144
8877	UCCAAACUACAUGAGUAU	494	8877	UCCAAACUACAUGAGUAU	494	8895	UACUCUAUGAUUUUGGAA	2145
8895	UAGUAAUUUUGCUACCCUCU	495	8895	UAGUAAUUUUGCUACCCUCU	495	8913	AGAGUAGCAAAUACUUA	2146
8913	UGCUGCGUUCUUGCUGCU	496	8913	UGCUGCGUUCUUGCUGCU	496	8931	AGCAGCAAGAACGCAAGCA	2147
8931	UGAGUGUACAUAUUUUAAG	497	8931	UGAGUGUACAUAUUUUAAG	497	8949	CUUAAAAUUGUACACUUA	2148
8949	GGAUGCUAUGGGCAACCCU	498	8949	GGAUGCUAUGGGCAACCCU	498	8967	AGGUUUUGCCCAUAGCAUCC	2149

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8967	UGUGCCAUUUGUUAUGAC	499	8967	UGUGCCAUUUGUUAUGAC	499	8985	GUCAUAAACAAUUGGCACA	2150
8985	CACUAAUUGCUAGAGGCU	500	8985	CACUAAUUGCUAGAGGCU	500	9003	ACCCUUAAGCAAAUUGG	2151
9003	UUCUAAUUCUUAUAGAG	501	9003	UUCUAAUUCUUAUAGAG	501	9021	CUCACUAAAGAAUAGAA	2152
9021	GUUCUGUCCAGACUCGU	502	9021	GUUCUGUCCAGACUCGU	502	9039	ACGAGUGUCGAGCAAGC	2153
9039	UUUGUGCUUAUGGAUGGU	503	9039	UUUGUGCUUAUGGAUGGU	503	9057	ACCAUCCAAAGCACAUA	2154
9057	UUCCAUCUACAGUUCU	504	9057	UUCCAUCUACAGUUCU	504	9075	AGGAACUUGUAUGUGAA	2155
9075	UAACAUUACUGGAGGCU	505	9075	UAACAUUACUGGAGGCU	505	9093	ACCCUACAGUAAUGUUA	2156
9093	UUCUGUAGAGUAGUACA	506	9093	UUCUGUAGAGUAGUACA	506	9111	UGUUAUACUUAACAGAA	2157
9111	AACUUUUGAUGCUGAGUAC	507	9111	AACUUUUGAUGCUGAGUAC	507	9129	GUACUCAGCAUCAAAGUU	2158
9129	CUUGAGAGUAGUAGUAC	508	9129	CUUGAGAGUAGUAGUAC	508	9147	GCAUGUACAUUCUACAG	2159
9147	CGAAAGGUCAGAGUAGGU	509	9147	CGAAAGGUCAGAGUAGGU	509	9165	ACCUACUUCUGACCUUUCG	2160
9165	UAUUGCCUACUACAGU	510	9165	UAUUGCCUACUACAGU	510	9183	ACUGGUAAGUAGGCAAAU	2161
9183	UGGUAAGUUGGUUUAU	511	9183	UGGUAAGUUGGUUUAU	511	9201	AUUAAGACCCAUUAACCA	2162
9201	UAUAGAGUUAACAGAGCU	512	9201	UAUAGAGUUAACAGAGCU	512	9219	AGCUCUGUAUUGCUCAUUA	2163
9219	UCUACAGGAGUUAUCUGU	513	9219	UCUACAGGAGUUAUCUGU	513	9237	ACAGAAACUCCUGUAAGA	2164
9237	UGGUGUAGUAGUAGAAU	514	9237	UGGUGUAGUAGUAGAAU	514	9255	AUUCUCCGCAUCAAACCA	2165
9255	UCUCUAGCUAAACUUAU	515	9255	UCUCUAGCUAAACUUAU	515	9273	AAAGUUGUAGCUAUGAGA	2166
9273	UACUCUUCUUGGCAACCU	516	9273	UACUCUUCUUGGCAACCU	516	9291	AGGUUGCACAAGAGGAGUA	2167
9291	UGUGGGUUCUUAAGUUGU	517	9291	UGUGGGUUCUUAAGUUGU	517	9309	CACAUUAAAGCACCACA	2168
9309	GUCUGCUUACUAGUGGCU	518	9309	GUCUGCUUACUAGUGGCU	518	9327	AGCCAUUACUGAAGCAGAC	2169
9327	UGGUGGUAUUAUUGCCAU	519	9327	UGGUGGUAUUAUUGCCAU	519	9345	UAUGGCAUUAUUAACCA	2170
9345	AUUGGUGACUUGGUGGCC	520	9345	AUUGGUGACUUGGUGGCC	520	9363	GGCAGCACAAGUCACCAU	2171
9363	CUACUACUUAUUGAAUUC	521	9363	CUACUACUUAUUGAAUUC	521	9381	GAUUUUAUUAAGUAGUAG	2172
9381	CAGACGUGUUAUUGGUGAG	522	9381	CAGACGUGUUAUUGGUGAG	522	9399	CUCACAAAACACGUCUG	2173
9399	GUACAACCAUGUUGUUGCU	523	9399	GUACAACCAUGUUGUUGCU	523	9417	AGCAACAACUUGGUUAGC	2174
9417	UGCUAAGCACAUIUUGUUA	524	9417	UGCUAAGCACAUIUUGUUA	524	9435	AAACAAAAGUGCAUUAAGCA	2175
9435	UUUGAUGUCUUAUCACUUA	525	9435	UUUGAUGUCUUAUCACUUA	525	9453	UAUAGUGAAGAGACAUAAA	2176
9453	ACUCUGUCUGGUACCGCU	526	9453	ACUCUGUCUGGUACCGCU	526	9471	AGCUGGUACCCAGACAGAGU	2177
9471	UUACAGCUUUCUGCCGGA	527	9471	UUACAGCUUUCUGCCGGA	527	9489	UCCCGCAGAAAGCUGUUA	2178
9489	AGUCUACUCAGCUUUUAC	528	9489	AGUCUACUCAGCUUUUAC	528	9507	GUAAAAGACUGAGUAGAU	2179
9507	CUUGUACUUGACAUUUAU	529	9507	CUUGUACUUGACAUUUAU	529	9525	AUAGAUGUCAAGUACAAG	2180
9525	UUUACCAUUGAUUUUA	530	9525	UUUACCAUUGAUUUUA	530	9543	UGAAACAUUUGGUUAGAA	2181
9543	AUUCUUGGCUACCUUUA	531	9543	AUUCUUGGCUACCUUUA	531	9561	UUGAAGGUGAGCCCAAGAU	2182
9561	AUGGUUUGCCAUUUUUCU	532	9561	AUGGUUUGCCAUUUUUCU	532	9579	AGAAAACUUGGCAACCAU	2183
9579	UCCUUAUUGGCCUUUUUGG	533	9579	UCCUUAUUGGCCUUUUUGG	533	9597	CCAAAAGGCAUUAAGGA	2184
9597	GAUAAACAGCAUUAUGUA	534	9597	GAUAAACAGCAUUAUGUA	534	9615	UACAUAGAUUGCUGUUAUC	2185
9615	AUUCUGUAUUCUCUGAAG	535	9615	AUUCUGUAUUCUCUGAAG	535	9633	CUUCAGAGAAAUAACAGAAU	2186
9633	GCACUGCCAUUGGUUUCU	536	9633	GCACUGCCAUUGGUUUCU	536	9651	AAAGAACCACUUGCAGUGC	2187
9651	UAACAACUACUUAAGGAA	537	9651	UAACAACUACUUAAGGAA	537	9669	UUUCCUAAGAUAGUUAUUA	2188
9669	AAGAGUCAUUAUUAUGGA	538	9669	AAGAGUCAUUAUUAUGGA	538	9687	UCCAUUAACAUAGACUCUU	2189
9687	AGUUAACUUAUAGACCUUC	539	9687	AGUUAACUUAUAGACCUUC	539	9705	GAAGGUACUAAUUAUUAACU	2190
9705	CGAGGAGGCGUUAUUGU	540	9705	CGAGGAGGCGUUAUUGU	540	9723	ACACAAAGCAGCCUCCUCCG	2191

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9723	UACCUUUUUUGCUACAAG	541	9723	UACCUUUUUUGCUACAAG	541	9741	CUUUGUUGAGCAAAAAGGUA	2192
9741	GGAAUUGUACCUAAAUIUG	542	9741	GGAAUUGUACCUAAAUIUG	542	9759	CAUUUUUAGGUACAUUUC	2193
9759	GCGUAGCGAGACAGUUG	543	9759	GCGUAGCGAGACAGUUG	543	9777	CAACAGUGUCUGCGUACGC	2194
9777	GCCAUUACACAGUAUAC	544	9777	GCCAUUACACAGUAUAC	544	9795	GUUUAUCUGUGUAAGUGGC	2195
9795	CAGGUUUCUGCUUAU	545	9795	CAGGUUUCUGCUUAU	545	9813	AUUAAGAGCAAGAUACCU	2196
9813	UAACAAGUACAAGUAUUC	546	9813	UAACAAGUACAAGUAUUC	546	9831	GAAUACUUGUAUUUUUA	2197
9831	CAGUGGAGCUUAGAUACU	547	9831	CAGUGGAGCUUAGAUACU	547	9849	AGUAUCUAAAGGCUCCACUG	2198
9849	UACGAGCUUUGUAGGCA	548	9849	UACGAGCUUUGUAGGCA	548	9867	UGUUCACGUAJUGUGGUA	2199
9867	AGCUUGCUGCCACUUAAGCA	549	9867	AGCUUGCUGCCACUUAAGCA	549	9885	UGCUAAGUGGCAGCAAGCU	2200
9885	AAAGGCUCUAAUAGCUUU	550	9885	AAAGGCUCUAAUAGCUUU	550	9903	AAAGCUUUUAGAGCCUUU	2201
9903	UAGCAACUCAGGUGCUAU	551	9903	UAGCAACUCAGGUGCUAU	551	9921	AUCAGCACCUAGAGUUGCUA	2202
9921	UGUUCUCUACCAACCCACA	552	9921	UGUUCUCUACCAACCCACA	552	9939	UGGUGGUUGGUAGAGAACCA	2203
9939	ACAGACAUCAUACUUCU	553	9939	ACAGACAUCAUACUUCU	553	9957	AGAAUGUAUUGAUUGUCUGU	2204
9957	UGCUGUUCUGCAGAGUGGU	554	9957	UGCUGUUCUGCAGAGUGGU	554	9975	ACCACUCUGCAGAACAGCA	2205
9975	UUUUAAGGAAUUGGCAUUC	555	9975	UUUUAAGGAAUUGGCAUUC	555	9993	GAAUGCCAUUUUCCUAAA	2206
9993	CCCGUCAGGCAAGUUGAA	556	9993	CCCGUCAGGCAAGUUGAA	556	10011	UUCAACUUGCCUGACGGG	2207
10011	AGGUGCAUGGUACAAGUA	557	10011	AGGUGCAUGGUACAAGUA	557	10029	UACUUGUACCAUGCACCCU	2208
10029	AAGCUGUGGAUACAACU	558	10029	AAGCUGUGGAUACAACU	558	10047	AGUUGUAGUUCACAGGCU	2209
10047	UCUUAUUGGUUGUGUGU	559	10047	UCUUAUUGGUUGUGUGU	559	10065	CAACCACAAUCCAUUAAGA	2210
10065	GGAUGACACAGUAUACUGU	560	10065	GGAUGACACAGUAUACUGU	560	10083	ACAGUAUACUGUGUACUCC	2211
10083	UCCAAAGCAUGUAUUGC	561	10083	UCCAAAGCAUGUAUUGC	561	10101	GCAUUGUACUUGUUGGA	2212
10101	CACAGCAGAAUAGGUAU	562	10101	CACAGCAGAAUAGGUAU	562	10119	AGCAUGUUCUUGUUGUG	2213
10119	UAUCCUAACUAUAGGAU	563	10119	UAUCCUAACUAUAGGAU	563	10137	AUCUUAUAGUUAAGGAUA	2214
10137	UCUGCUCAUUGGCAUUC	564	10137	UCUGCUCAUUGGCAUUC	564	10155	GGAUUUGGAAUAGAGCA	2215
10155	CAACCAUAGCUUUCUUGU	565	10155	CAACCAUAGCUUUCUUGU	565	10173	AACAAGAAAGCUAUGGUUG	2216
10173	UCAGGCGUGGCAUUGUCAA	566	10173	UCAGGCGUGGCAUUGUCAA	566	10191	UUGAACAUUGCCAGCCUGA	2217
10191	ACUUCGUGUUAUUGGCAU	567	10191	ACUUCGUGUUAUUGGCAU	567	10209	AUGGCCAAUAAACAGGAU	2218
10209	UUCUAUGCAAAUUGUCUG	568	10209	UUCUAUGCAAAUUGUCUG	568	10227	CAGCAAAUUUUGCAUAGAA	2219
10227	GCUUAGGCUUAAAGUUGAU	569	10227	GCUUAGGCUUAAAGUUGAU	569	10245	AUCAACUUAAGCCUAAGC	2220
10245	UACUUCUAAACCUAAGACA	570	10245	UACUUCUAAACCUAAGACA	570	10263	UGUCUUAAGGUUAAGAAUA	2221
10263	ACCCAAGUAUAAUUGUC	571	10263	ACCCAAGUAUAAUUGUC	571	10281	GACAAUUUAUACUUGGU	2222
10281	CCGUUACCAACCGUGUCAA	572	10281	CCGUUACCAACCGUGUCAA	572	10299	UUGACCAGGUUGGUAACGG	2223
10299	AACAUUUUACAGUUAAGCA	573	10299	AACAUUUUACAGUUAAGCA	573	10317	UGCUAGAACUAGAAUUGU	2224
10317	AUGCUACAAGUUGUACCCA	574	10317	AUGCUACAAGUUGUACCCA	574	10335	UGGUAACCAUUGUAGCAU	2225
10335	AUCUGGUGUUUAUCAGUGU	575	10335	AUCUGGUGUUUAUCAGUGU	575	10353	ACACUGAUAAACACCCAGU	2226
10353	UGCCAUAGAGACCUUAUACU	576	10353	UGCCAUAGAGACCUUAUACU	576	10371	AUGAUUAGGUUAGUAGCA	2227
10371	UACCAUUAAGGUUCUUC	577	10371	UACCAUUAAGGUUCUUC	577	10389	GAAAGAACCUUUAUUGUA	2228
10389	CCUUAUUGGAUACUUGGU	578	10389	CCUUAUUGGAUACUUGGU	578	10407	ACCACAUAGUACUUAAGG	2229
10407	UAGUUGGUGUUUAACAU	579	10407	UAGUUGGUGUUUAACAU	579	10425	AUGUUAACCAACACUA	2230
10425	UGAUUAUAGUUGGUGUCU	580	10425	UGAUUAUAGUUGGUGUCU	580	10443	AGACGCAUUAUUAUUA	2231
10443	UUUCUGCUUAUAGUACAU	581	10443	UUUCUGCUUAUAGUACAU	581	10461	AUGAUGCAUUAAGCAGAA	2232
10461	UAUGGAGCUUCCAAACAGGA	582	10461	UAUGGAGCUUCCAAACAGGA	582	10479	UCCUGUUGGAAGCUCCAU	2233

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10479	AGUACACGCGUACUGAC	583	10479	AGUACACGCGUACUGAC	583	10497	GUACAGUACCGGUGUACU	2234
10497	CUUAGAAAGGUAAUUCUUA	584	10497	CUUAGAAAGGUAAUUCUUA	584	10515	AUAGAAUUIUACCUUUAAG	2235
10515	UGGUCUUAUUGUUGACAGA	585	10515	UGGUCUUAUUGUUGACAGA	585	10533	UCUGUCAAACAAUUGGACCA	2236
10533	ACAAACUGCACAGGUGCA	586	10533	ACAAACUGCACAGGUGCA	586	10551	UGCAGCCUGUGCAGUUGU	2237
10551	AGGUACAGACACAAACUA	587	10551	AGGUACAGACACAAACUA	587	10569	UAUGGUUGUGUCUGUACCU	2238
10569	AACAUUAAUUGUUUGGCA	588	10569	AACAUUAAUUGUUUGGCA	588	10587	UGCCAAACAAUUAUUGUU	2239
10587	AUGGCUUUGUGUGUGUU	589	10587	AUGGCUUUGUGUGUGUU	589	10605	AACAGCAGCAUACAGCCAU	2240
10605	UAUCAAUGGUGAUGGUGG	590	10605	UAUCAAUGGUGAUGGUGG	590	10623	CCAGCUUACCAUUGUAUA	2241
10623	GUUUCUUAUAGAUUACCC	591	10623	GUUUCUUAUAGAUUACCC	591	10641	GGUGAAUCUUAJAGAAAC	2242
10641	CACUACUUAUGAUGACUUU	592	10641	CACUACUUAUGAUGACUUU	592	10659	AAAGUCAUUAAGAGUAGUG	2243
10659	UAACCUUGUGGCAUUGAAG	593	10659	UAACCUUGUGGCAUUGAAG	593	10677	CUUACUUGCCACAAGGUUA	2244
10677	GUACAACUUAAGACCUUUG	594	10677	GUACAACUUAAGACCUUUG	594	10695	CAAAGGUCAUAGUUGUAC	2245
10695	GACACAAGAUUGUUGAC	595	10695	GACACAAGAUUGUUGAC	595	10713	GUACAAGUAGUUGUGUC	2246
10713	CAUUAUUGGACCUUUCU	596	10713	CAUUAUUGGACCUUUCU	596	10731	AGAAAGGUGCCAAUUG	2247
10731	UGCUCAACAGGAUUGCC	597	10731	UGCUCAACAGGAUUGCC	597	10749	GGCAAUCCUUGUUUGACA	2248
10749	CGUCUUAUUGUGUGCU	598	10749	CGUCUUAUUGUGUGCU	598	10767	AGCACACAUUUAAGACG	2249
10767	UGCUUUGAAAGAGUGUGU	599	10767	UGCUUUGAAAGAGUGUGU	599	10785	CAGCAGCUCUUUCAAAGCA	2250
10785	GCAGAAUGGUAGUUGGU	600	10785	GCAGAAUGGUAGUUGGU	600	10803	ACCAUUAUCCAUUUGUC	2251
10803	UCGUACUUAUUGGUGAC	601	10803	UCGUACUUAUUGGUGAC	601	10821	GUACCAAGGAUAGUACGA	2252
10821	CACUUAUUAAGAGUAG	602	10821	CACUUAUUAAGAGUAG	602	10839	CUCAUUCUUAUUAUUGUG	2253
10839	GUUUAACCAUUAUUGU	603	10839	GUUUAACCAUUAUUGU	603	10857	AACACAAUUGUGUUAAC	2254
10857	UGUUAACCAUUGUGU	604	10857	UGUUAACCAUUGUGU	604	10875	ACCAGAGCAUUGUUAACA	2255
10875	UGUUAACCUUCCAGGUAAG	605	10875	UGUUAACCUUCCAGGUAAG	605	10893	CUUACCUUGGAAGGUAACA	2256
10893	GUUUAAGAAUUGUUAAG	606	10893	GUUUAAGAAUUGUUAAG	606	10911	CUUUAACAAUUAUUGUAAC	2257
10911	GGGCACUUAUUGGUAUG	607	10911	GGGCACUUAUUGGUAUG	607	10929	CAUCCAAUUAUUGAGUCCG	2258
10929	GUUUAACUUAUUGGUAUG	608	10929	GUUUAACUUAUUGGUAUG	608	10947	UGUAAGAAAGUUAUUAAGC	2259
10947	AUCACUUAUUGUUAUUG	609	10947	AUCACUUAUUGUUAUUG	609	10965	AACAAGAAUUAUUAUUAAG	2260
10965	UCAAAGUACACAGUGGUA	610	10965	UCAAAGUACACAGUGGUA	610	10983	UGACCAUUGUGUUAUUAAG	2261
10983	ACUGUUAUUAUUGUUAAC	611	10983	ACUGUUAUUAUUGUUAAC	611	11001	GUAAACAAAGAAUUAUUAAG	2262
11001	CGAGAAUGCUUUAUUGCCA	612	11001	CGAGAAUGCUUUAUUGCCA	612	11019	UGGCAAGAAAGCAUUAUUAAG	2263
11019	AUUAACUUAUUGGUAUUAUG	613	11019	AUUAACUUAUUGGUAUUAUG	613	11037	CAUUAACCAAGAGUUAUUAAG	2264
11037	GGCAAUUGCUGCAUUGGCU	614	11037	GGCAAUUGCUGCAUUGGCU	614	11055	AGCACAUUGCAGCAUUAUUAAG	2265
11055	UAUGCUGCUUAUUAAGCAU	615	11055	UAUGCUGCUUAUUAAGCAU	615	11073	AUGCUUAACAAAGCAUUAUUAAG	2266
11073	UAAGCACGCAUUAUUGGCU	616	11073	UAAGCACGCAUUAUUGGCU	616	11091	GCACAAAGAAUUGGUGUUA	2267
11091	CUUUAUUAUUGGUAUUAUG	617	11091	CUUUAUUAUUGGUAUUAUG	617	11109	AGAAGGUAACAGAAUUAAG	2268
11109	UCUUGCAACAGUUGUUAAC	618	11109	UCUUGCAACAGUUGUUAAC	618	11127	GUAGCAUUAUUGGUAUUAAG	2269
11127	CUUUAUUAUUGGUAUUAUG	619	11127	CUUUAUUAUUGGUAUUAUG	619	11145	CAUGUAGCAUUAUUAUUAAG	2270
11145	GCCUGUAGCUGGUGUUAUG	620	11145	GCCUGUAGCUGGUGUUAUG	620	11163	CAUACCCAGCAGUUAUUAAG	2271
11163	GCUGAUCUUAUUGGUGCU	621	11163	GCUGAUCUUAUUGGUGCU	621	11181	AAGCAUUAUUAUUAUUAAG	2272
11181	UGAAUUGGUGUUAUUAUG	622	11181	UGAAUUGGUGUUAUUAUG	622	11199	GUAGUGUUAUUAUUAUUAAG	2273
11199	CUUGUCUGGUAUUAUUAUG	623	11199	CUUGUCUGGUAUUAUUAUG	623	11217	AAGCUUAUUAUUAUUAUUAAG	2274
11217	UAAGGAUUGGUAUUAUUAUG	624	11217	UAAGGAUUGGUAUUAUUAUG	624	11235	AUACAUAACAAUUAUUAUUAAG	2275

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11235	UGCUUACGCUUUAGUUUG	625	11235	UGCUUACGCUUUAGUUUG	625	11253	CAAAACUAAAGCUGAAGCA	2276
11253	GCUUUUUUCUAGACGCU	626	11253	GCUUUUUUCUAGACGCU	626	11271	AGCUGUCAUGAGAAUAGC	2277
11271	UGCGACUGUUUAUGAUG	627	11271	UGCGACUGUUUAUGAUG	627	11289	AUCAUCAAACAGUCGCGA	2278
11289	UGCGACUGAGGUGUUUG	628	11289	UGCGACUGAGGUGUUUG	628	11307	CCAAACACGUCUAGACGCA	2279
11307	GACACUGAUGAAUGCAUU	629	11307	GACACUGAUGAAUGCAUU	629	11325	AAUGACAUCUACAGUGUC	2280
11325	UACACUUGUUUACAAAGUC	630	11325	UACACUUGUUUACAAAGUC	630	11343	GACUUUGUAAACAGUGUA	2281
11343	CUACUAGGUAUUGCUUA	631	11343	CUACUAGGUAUUGCUUA	631	11361	UAAAGCAUUAACCAUAGUAG	2282
11361	AGAUAAGCUUUUCCUAG	632	11361	AGAUAAGCUUUUCCUAG	632	11379	GAUGGAAUAAGCUUUGAUCU	2283
11379	GUGGGCUUAGUAUUUCU	633	11379	GUGGGCUUAGUAUUUCU	633	11397	AGAAUAACUAAGGCCAC	2284
11397	UGUAACCUUAACUAUUCU	634	11397	UGUAACCUUAACUAUUCU	634	11415	AGAAUAGUUAAGGUUACA	2285
11415	UGGUGUCGUUACGACUAC	635	11415	UGGUGUCGUUACGACUAC	635	11433	GAUAGUCGUUACGACACCA	2286
11433	CAUGUUUUUAGCUAGGCU	636	11433	CAUGUUUUUAGCUAGGCU	636	11451	AGCUCUAGCUAAAAACAUG	2287
11451	UAUAGUUGUUGUGUGUU	637	11451	UAUAGUUGUUGUGUGUU	637	11469	AACACACACAAACACUUA	2288
11469	UGAGUAUUACCAUUGUA	638	11469	UGAGUAUUACCAUUGUA	638	11487	UAACAAUGGGUAAUACUCA	2289
11487	AUUUAUACUGGCAACAC	639	11487	AUUUAUACUGGCAACAC	639	11505	GGUGUUGCCAGUAAUAAU	2290
11505	CUUACAGUGUAUCGCUU	640	11505	CUUACAGUGUAUCGCUU	640	11523	AAGCAUGAUACACUGUAAG	2291
11523	UGUUUUUUGCUUAGGC	641	11523	UGUUUUUUGCUUAGGC	641	11541	GCCUAAAGAAACAAUAA	2292
11541	CUUUUUUUGCUGCUAC	642	11541	CUUUUUUUGCUGCUAC	642	11559	GUAGCAGCAGCAACAAUAG	2293
11559	CUUUGGCCUUUUCUGUUUA	643	11559	CUUUGGCCUUUUCUGUUUA	643	11577	UAAACAGAAAGGCCAAAG	2294
11577	ACUACACCGUUAUCUAGG	644	11577	ACUACACCGUUAUCUAGG	644	11595	CCUGAAGUAACGGUUGAGU	2295
11595	GUUACCUUUGGUGUUUAU	645	11595	GUUACCUUUGGUGUUUAU	645	11613	AUAACACCAAGAGUAAGC	2296
11613	UGUACUUCUGGUCUAC	646	11613	UGUACUUCUGGUCUAC	646	11631	UUAAGACCAAGUAGUCA	2297
11631	ACAAGAAUUAGGUUAUG	647	11631	ACAAGAAUUAGGUUAUG	647	11649	CAUUAACCUAAAUUCUUGU	2298
11649	GAACUCCAGGGGCUUUG	648	11649	GAACUCCAGGGGCUUUG	648	11667	CAAAAGCCCGGGGAGUUC	2299
11667	GCCUCCUAAAGAGUAUU	649	11667	GCCUCCUAAAGAGUAUU	649	11685	AUAUCUACUUAAGGAGGC	2300
11685	UGAUGCUUUAAGCUUAA	650	11685	UGAUGCUUUAAGCUUAA	650	11703	GUUAAGCUUUAAGGCAUCA	2301
11703	CAUUAAGUUUGGGUAUU	651	11703	CAUUAAGUUUGGGUAUU	651	11721	AUAACCCAAACCUUAAUG	2302
11721	UGGAGGUAACCAUGUAUC	652	11721	UGGAGGUAACCAUGUAUC	652	11739	GAUACAUGGUUUUACCUCCA	2303
11739	CAAGGUUGCUUACUACAG	653	11739	CAAGGUUGCUUACUACAG	653	11757	CUGUACAGUAGCAACCUUG	2304
11757	GUCUAAAUGUCUGACGUA	654	11757	GUCUAAAUGUCUGACGUA	654	11775	UACGUCAGACAUUUUAGAC	2305
11775	AAAGUGCACAUUCUGGUA	655	11775	AAAGUGCACAUUCUGGUA	655	11793	UACCAACAGUUGCAGUUCU	2306
11793	ACUGCUCUGGUUUCUCAA	656	11793	ACUGCUCUGGUUUCUCAA	656	11811	UUGAAGAACCCGAGAGCAGU	2307
11811	ACAACUAGAGUAGUCA	657	11811	ACAACUAGAGUAGUCA	657	11829	UGACUCUACUUAAGUUGU	2308
11829	AUCUUCUAAAUUGGGCA	658	11829	AUCUUCUAAAUUGGGCA	658	11847	UGCCCAACAUUUAAGAGAU	2309
11847	ACAAUGUGUACAACUCCAC	659	11847	ACAAUGUGUACAACUCCAC	659	11865	GUGGAGUUUUAACAUUUGU	2310
11865	CAUUGAUUUUCUUCUGCA	660	11865	CAUUGAUUUUCUUCUGCA	660	11883	UGCAAGAAAGAAUUAUUAUG	2311
11883	AAAGACACACUGAAGCU	661	11883	AAAGACACACUGAAGCU	661	11901	AGCUACAGUUGUGUCUUUU	2312
11901	UUUCGAGAGAGUUGGUUCU	662	11901	UUUCGAGAGAGUUGGUUCU	662	11919	AGAAACCAUCUUCUCGAA	2313
11919	UCUUUGCUGUUUUUGCUA	663	11919	UCUUUGCUGUUUUUGCUA	663	11937	UAGCAAAACAGACAAAGA	2314
11937	UCCUACUGAGGUGGUGUA	664	11937	UCCUACUGAGGUGGUGUA	664	11955	UACGACCCUGGAGUAGAU	2315
11955	AGACAUUAAUAGGUUGUC	665	11955	AGACAUUAAUAGGUUGUC	665	11973	GCACACCCUUAUUAUUGUCU	2316
11973	CGAGGAAUUGCUGAUAAC	666	11973	CGAGGAAUUGCUGAUAAC	666	11991	GUUAUCGAGCAUUUCCUGC	2317

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11991	CCGUGCUACUCUACGGCU	667	11991	CCGUGCUACUCUACGGCU	667	12009	AGCCUGAAGAGUAGCAGG	2318
12009	UAUUGCUUCAGAAUUAU	668	12009	UAUUGCUUCAGAAUUAU	668	12027	ACUAAUUCUGAAGCAUA	2319
12027	UUCUUUACCAUAUAGCC	669	12027	UUCUUUACCAUAUAGCC	669	12045	GGCAUUAUGGUAAGAA	2320
12045	CGCUUAUGCCACUGCCAG	670	12045	CGCUUAUGCCACUGCCAG	670	12063	CUGGGCAGUGGUAAGCG	2321
12063	GGAGGCCUAUGAGCAGCU	671	12063	GGAGGCCUAUGAGCAGCU	671	12081	AGCCUGCUAUGGCCUCC	2322
12081	UGUAGCUAUGGUAUUCU	672	12081	UGUAGCUAUGGUAUUCU	672	12099	AGAAUCCCAUUAAGCUACA	2323
12099	UGAAGUCGUUCUCAAAG	673	12099	UGAAGUCGUUCUCAAAG	673	12117	CUUUUGAGAACGACUUA	2324
12117	GUUAAAGAAUCUUUAAU	674	12117	GUUAAAGAAUCUUUAAU	674	12135	AUCAAAGAUUUUUUAAC	2325
12135	UGUGGCUAAUCUGAGUUU	675	12135	UGUGGCUAAUCUGAGUUU	675	12153	AAUCAGAGUUUAAGCCACA	2326
12153	UGACCGUGAUGGCGCAUG	676	12153	UGACCGUGAUGGCGCAUG	676	12171	CAUGGCAGCAUCACGGUCA	2327
12171	GCAACGCAAGUUGGAAAG	677	12171	GCAACGCAAGUUGGAAAG	677	12189	CUUUUCCACUUGCGUUGC	2328
12189	GAUGGCAGUACGGCUAUG	678	12189	GAUGGCAGUACGGCUAUG	678	12207	CAUAGCCAUUUUGGGUC	2329
12207	GACCCAAUUGUACAAACAG	679	12207	GACCCAAUUGUACAAACAG	679	12225	CUGUUUGUACAUUUUGGUC	2330
12225	GGCAAGAUUCGAGGACAAG	680	12225	GGCAAGAUUCGAGGACAAG	680	12243	CUUUGCCUGAGAUUUGCC	2331
12243	GAGGCAAAUUAACUAGU	681	12243	GAGGCAAAUUAACUAGU	681	12261	ACUAGUUAUUUUUGCCUC	2332
12261	UGCUAUGCAAAUAGCUC	682	12261	UGCUAUGCAAAUAGCUC	682	12279	GAGCAUUGUUUGCAUAGCA	2333
12279	CUUCACUAUGCUUAGGAAAG	683	12279	CUUCACUAUGCUUAGGAAAG	683	12297	CUUCCUAAAGCAUAGUAGG	2334
12297	GUUUAUUAUUAUUAUUAU	684	12297	GUUUAUUAUUAUUAUUAU	684	12315	AAGUGCAUUAUUAUUAUUAU	2335
12315	UAACAACAUUAUUAUUAU	685	12315	UAACAACAUUAUUAUUAU	685	12333	AUUGUUAUUAUUAUUAUUAU	2336
12333	UGCGGUGAUGGUUGUUGU	686	12333	UGCGGUGAUGGUUGUUGU	686	12351	AACCAACCAUUAUUAUUAU	2337
12351	UCCACUUAUUAUUAUUAU	687	12351	UCCACUUAUUAUUAUUAU	687	12369	UGGUAUUAUUAUUAUUAU	2338
12369	AUUGACUACAGCAGCCAAA	688	12369	AUUGACUACAGCAGCCAAA	688	12387	UUUGGUGUGUUAUUAUUAU	2339
12387	ACUCAUGGUUGUUGUCCCU	689	12387	ACUCAUGGUUGUUGUCCCU	689	12405	AGGCAACCAUUAUUAUUAU	2340
12405	UGAUUAUGGUUUAUUAUUAU	690	12405	UGAUUAUGGUUUAUUAUUAU	690	12423	CUUUAUUAUUAUUAUUAUUAU	2341
12423	GAACACUUAUUAUUAUUAU	691	12423	GAACACUUAUUAUUAUUAU	691	12441	GUUUAUUAUUAUUAUUAUUAU	2342
12441	CACCUUAUUAUUAUUAUUAU	692	12441	CACCUUAUUAUUAUUAUUAU	692	12459	AGAUUAUUAUUAUUAUUAUUAU	2343
12459	UGCACUCUGGGAUUAUUAU	693	12459	UGCACUCUGGGAUUAUUAU	693	12477	CUGGAUUAUUAUUAUUAUUAU	2344
12477	GCAAGAUUAUUAUUAUUAU	694	12477	GCAAGAUUAUUAUUAUUAU	694	12495	AUCCGCAUUAUUAUUAUUAUUAU	2345
12495	UAGCAAGAUUAUUAUUAUUAU	695	12495	UAGCAAGAUUAUUAUUAUUAU	695	12513	AAGUUAUUAUUAUUAUUAUUAU	2346
12513	UAGUUAUUAUUAUUAUUAUUAU	696	12513	UAGUUAUUAUUAUUAUUAUUAU	696	12531	GUCCAUUAUUAUUAUUAUUAUUAU	2347
12531	CAAUUCCCAUUAUUAUUAUUAU	697	12531	CAAUUCCCAUUAUUAUUAUUAU	697	12549	AGCCAAUUAUUAUUAUUAUUAUUAU	2348
12549	UUGGCCUUAUUAUUAUUAUUAU	698	12549	UUGGCCUUAUUAUUAUUAUUAU	698	12567	UGUAACAAUUAUUAUUAUUAUUAUUAU	2349
12567	AGCUCUAAGAGCCCAUUAUUAU	699	12567	AGCUCUAAGAGCCCAUUAUUAU	699	12585	UGAGUUGGCUUAUUAUUAUUAUUAUUAU	2350
12585	AGCUGUUAUUAUUAUUAUUAUUAU	700	12585	AGCUGUUAUUAUUAUUAUUAUUAU	700	12603	AUUCUGAUGUUAUUAUUAUUAUUAUUAU	2351
12603	UAUUAUUAUUAUUAUUAUUAUUAU	701	12603	UAUUAUUAUUAUUAUUAUUAUUAU	701	12621	UACUGGACUUAUUAUUAUUAUUAUUAUUAU	2352
12621	AGCACUACGACAGAUUAUUAUUAUUAU	702	12621	AGCACUACGACAGAUUAUUAUUAUUAU	702	12639	GGACAUCUGUGUUAUUAUUAUUAUUAUUAU	2353
12639	CUUGCGGCGUUAUUAUUAUUAUUAUUAU	703	12639	CUUGCGGCGUUAUUAUUAUUAUUAUUAU	703	12657	UGUGUUAUUAUUAUUAUUAUUAUUAUUAU	2354
12657	ACAAACGCUUAUUAUUAUUAUUAUUAUUAU	704	12657	ACAAACGCUUAUUAUUAUUAUUAUUAUUAU	704	12675	AUCAGCAAGCGUUAUUAUUAUUAUUAUUAUUAU	2355
12675	UGACAUAUUAUUAUUAUUAUUAUUAUUAUUAU	705	12675	UGACAUAUUAUUAUUAUUAUUAUUAUUAUUAU	705	12693	GUAGGCAAGCGUUAUUAUUAUUAUUAUUAUUAUUAU	2356
12693	CUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	706	12693	CUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	706	12711	UCCCUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2357
12711	AGGUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	707	12711	AGGUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	707	12729	UGCCAGCAAAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2358
12729	AUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	708	12729	AUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	708	12747	UUGGUGGUGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2359

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12747	AGAUCUCAAUUGGGCUAGA	709	12747	AGAUCUCAAUUGGGCUAGA	709	12765	UCUAGCCCAUUIUGAGUUCU	2360
12765	AUCCCUAAGAGUGAGU	710	12765	AUCCCUAAGAGUGAGU	710	12783	ACCAUCACUCUUAAGGAAU	2361
12783	UACAGGUACAUAUACACA	711	12783	UACAGGUACAUAUACACA	711	12801	UGUGAAUAUUGUACCUUUA	2362
12801	AGAACUGGAACCCUUGU	712	12801	AGAACUGGAACCCUUGU	712	12819	ACAAGGUGUUCUCCAUUCU	2363
12819	UAGGUUUGUUAACAGACACA	713	12819	UAGGUUUGUUAACAGACACA	713	12837	UGUGUCUGUAACAAACCUA	2364
12837	ACCAAAAGGGCUAAAGUG	714	12837	ACCAAAAGGGCUAAAGUG	714	12855	CACUUUAGGCCCUUUUGGU	2365
12855	GAAUAUACUUAUUAUUAU	715	12855	GAAUAUACUUAUUAUUAU	715	12873	GAUGAAUUAUUAUUAUUAU	2366
12873	CAAGGCUUAUUAUUAUUAU	716	12873	CAAGGCUUAUUAUUAUUAU	716	12891	UAGGUUUGUUAUUAUUAU	2367
12891	AAUAAGAGGUUUGGUGUG	717	12891	AAUAAGAGGUUUGGUGUG	717	12909	CAGCACAUAUUAUUAUUAU	2368
12909	GGGAGUUAUUAUUAUUAU	718	12909	GGGAGUUAUUAUUAUUAU	718	12927	UGUAGCAGUUAUUAUUAU	2369
12927	AGUACGUCUUAUUAUUAU	719	12927	AGUACGUCUUAUUAUUAU	719	12945	UCCAGCCUUAUUAUUAU	2370
12945	AAUUGUUAUUAUUAUUAU	720	12945	AAUUGUUAUUAUUAUUAU	720	12963	AGUACUUAUUAUUAUUAU	2371
12963	UGCCAAUUAUUAUUAUUAU	721	12963	UGCCAAUUAUUAUUAUUAU	721	12981	AAGCAGUUAUUAUUAUUAU	2372
12981	UUCUUAUUAUUAUUAUUAU	722	12981	UUCUUAUUAUUAUUAUUAU	722	12999	UGCAAAGCAGUUAUUAUUAU	2373
12999	AGUAGCCUUAUUAUUAUUAU	723	12999	AGUAGCCUUAUUAUUAUUAU	723	13017	UGCUUUAUUAUUAUUAUUAU	2374
13017	AUAUAGGUUAUUAUUAUUAU	724	13017	AUAUAGGUUAUUAUUAUUAU	724	13035	UGCUUUAUUAUUAUUAUUAU	2375
13035	AAGUGGAGGACAAUUAUUAU	725	13035	AAGUGGAGGACAAUUAUUAU	725	13053	GAUUGGUUAUUAUUAUUAUUAU	2376
13053	CACCAACUGUGUUAUUAUUAU	726	13053	CACCAACUGUGUUAUUAUUAU	726	13071	CAUUAUUAUUAUUAUUAUUAU	2377
13071	GUUGUGUUAUUAUUAUUAUUAU	727	13071	GUUGUGUUAUUAUUAUUAUUAU	727	13089	ACCAGUGUGUUAUUAUUAUUAU	2378
13089	UACAGGACGAAUUAUUAUUAU	728	13089	UACAGGACGAAUUAUUAUUAU	728	13107	AGUUAUUAUUAUUAUUAUUAU	2379
13107	UGUAAACAGGAAUUAUUAUUAU	729	13107	UGUAAACAGGAAUUAUUAUUAU	729	13125	GUUAGCUUAUUAUUAUUAUUAU	2380
13125	CAUGGACCAAGUUAUUAUUAUUAU	730	13125	CAUGGACCAAGUUAUUAUUAUUAU	730	13143	AAAGGACUUAUUAUUAUUAUUAU	2381
13143	UGUGUGUUAUUAUUAUUAUUAU	731	13143	UGUGUGUUAUUAUUAUUAUUAU	731	13161	ACAACUUAUUAUUAUUAUUAUUAU	2382
13161	UCUGUUAUUAUUAUUAUUAUUAU	732	13161	UCUGUUAUUAUUAUUAUUAUUAU	732	13179	GUGGACUUAUUAUUAUUAUUAUUAU	2383
13179	CAUUGACCAUUAUUAUUAUUAUUAU	733	13179	CAUUGACCAUUAUUAUUAUUAUUAU	733	13197	AGGAAUUAUUAUUAUUAUUAUUAU	2384
13197	UAAAGGAAUUAUUAUUAUUAUUAU	734	13197	UAAAGGAAUUAUUAUUAUUAUUAU	734	13215	CAAGUUAUUAUUAUUAUUAUUAUUAU	2385
13215	GAAAGGAAUUAUUAUUAUUAUUAU	735	13215	GAAAGGAAUUAUUAUUAUUAUUAU	735	13233	UUGGACGUAUUAUUAUUAUUAUUAUUAU	2386
13233	AAUACCUUAUUAUUAUUAUUAUUAU	736	13233	AAUACCUUAUUAUUAUUAUUAUUAU	736	13251	AGCACAAGUUAUUAUUAUUAUUAUUAUUAU	2387
13251	UAUAGACCCAGUUAUUAUUAUUAUUAU	737	13251	UAUAGACCCAGUUAUUAUUAUUAUUAU	737	13269	AAACCCAGUUAUUAUUAUUAUUAUUAUUAU	2388
13269	UACACUUAUUAUUAUUAUUAUUAUUAU	738	13269	UACACUUAUUAUUAUUAUUAUUAUUAU	738	13287	GACUGUUAUUAUUAUUAUUAUUAUUAUUAU	2389
13287	CUGUACCCUUAUUAUUAUUAUUAUUAUUAU	739	13287	CUGUACCCUUAUUAUUAUUAUUAUUAUUAU	739	13305	CAUUCGCAUUAUUAUUAUUAUUAUUAUUAU	2390
13305	GUGGAAAGGUUAUUAUUAUUAUUAUUAUUAU	740	13305	GUGGAAAGGUUAUUAUUAUUAUUAUUAUUAU	740	13323	ACAGCCAUUAUUAUUAUUAUUAUUAUUAUUAU	2391
13323	UAGUUGUUAUUAUUAUUAUUAUUAUUAUUAU	741	13323	UAGUUGUUAUUAUUAUUAUUAUUAUUAUUAU	741	13341	GCGGAGUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2392
13341	CGAACCCUUAUUAUUAUUAUUAUUAUUAUUAU	742	13341	CGAACCCUUAUUAUUAUUAUUAUUAUUAUUAU	742	13359	AGACUGUAUUAUUAUUAUUAUUAUUAUUAUUAU	2393
13359	UGCGGAGUUAUUAUUAUUAUUAUUAUUAUUAU	743	13359	UGCGGAGUUAUUAUUAUUAUUAUUAUUAUUAU	743	13377	AAACGUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2394
13377	UUUAAACGGUUAUUAUUAUUAUUAUUAUUAUUAU	744	13377	UUUAAACGGUUAUUAUUAUUAUUAUUAUUAUUAU	744	13395	CACCGCAAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2395
13395	GUAAGUGGAGUUAUUAUUAUUAUUAUUAUUAUUAU	745	13395	GUAAGUGGAGUUAUUAUUAUUAUUAUUAUUAUUAU	745	13413	UAGGACGGUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2396
13413	ACACCGUGGAGUUAUUAUUAUUAUUAUUAUUAUUAU	746	13413	ACACCGUGGAGUUAUUAUUAUUAUUAUUAUUAUUAU	746	13431	UAGCUGGAGUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2397
13431	ACUAGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	747	13431	ACUAGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	747	13449	AGAGGAGUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2398
13449	UACAGGCUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	748	13449	UACAGGCUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	748	13467	AAAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2399
13467	UACAACGAAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	749	13467	UACAACGAAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	749	13485	CAGCAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2400
13485	GGUUUUGCAAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	750	13485	GGUUUUGCAAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	750	13503	UUAGGAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAUUAU	2401

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13503	AAAACUAAUUGCUGCGCU	751	13503	AAAACUAAUUGCUGCGCU	751	13521	AGCGACAGCAAUUAGUUUU	2402
13521	UUCGAGGAGGAGGAGG	752	13521	UUCGAGGAGGAGGAGG	752	13539	CCUCAUCCUUCUGCGGAA	2403
13539	GAAGGCAUUUUUAGACU	753	13539	GAAGGCAUUUUUAGACU	753	13557	AGUCUAAUAAUUGCCUUC	2404
13557	UCUUAUUUGUAGUUAAGA	754	13557	UCUUAUUUGUAGUUAAGA	754	13575	UCUUAUUUGUAGUUAAGA	2405
13575	AGGCAUUAUUGUUAACU	755	13575	AGGCAUUAUUGUUAACU	755	13593	AGUUAAGACAUUAGUUGCCU	2406
13593	UACCAACAUGAAGAGACUA	756	13593	UACCAACAUGAAGAGACUA	756	13611	UAGUCUCUUAUUGUUGUA	2407
13611	AUUUAUAAUUGGUUAAG	757	13611	AUUUAUAAUUGGUUAAG	757	13629	CUUUAACCAAGUUAUAAU	2408
13629	GAUUGCAGCGGUUGCUG	758	13629	GAUUGCAGCGGUUGCUG	758	13647	CAGCAACCGCUGGACAAUC	2409
13647	GUCCAGUACUUUUAAGU	759	13647	GUCCAGUACUUUUAAGU	759	13665	ACUUAAGAAAGUCAUGGAC	2410
13665	UUUAGAGUAGUUGGAGAC	760	13665	UUUAGAGUAGUUGGAGAC	760	13683	UGUCACCAUCUACUCUAAA	2411
13683	AUGGUACCAUAUUAUCAC	761	13683	AUGGUACCAUAUUAUCAC	761	13701	GUGAUUAUUGUGGUACCAU	2412
13701	CGUCAGCGCUAAUUAU	762	13701	CGUCAGCGCUAAUUAU	762	13719	AUUUAGUUAGAGCGUGACG	2413
13719	UACCAAUUGGCUUAUUAAG	763	13719	UACCAAUUGGCUUAUUAAG	763	13737	CUAAAUACGCAUUGUGUA	2414
13737	GUCAUUGCUCUACGUAU	764	13737	GUCAUUGCUCUACGUAU	764	13755	AUAGACGUAGAGCAUAGAC	2415
13755	UUUGAUGAGGGUAAUUG	765	13755	UUUGAUGAGGGUAAUUG	765	13773	CACAAUUAACCCUCAUAAA	2416
13773	GAUACAUUAAAGAAUUA	766	13773	GAUACAUUAAAGAAUUA	766	13791	GUUUUUCUUUUUAAUGUAUC	2417
13791	CUCGUCACAUAAUUGCU	767	13791	CUCGUCACAUAAUUGCU	767	13809	AGCAUUAUUGUAGACGAG	2418
13809	UGUGAUUGAUUAUUAUUA	768	13809	UGUGAUUGAUUAUUAUUA	768	13827	UGAAUUAUUAUUAUUAU	2419
13827	AUUAAGAAAGAUUGGUU	769	13827	AUUAAGAAAGAUUGGUU	769	13845	CAUACCAUCCUUCUUAU	2420
13845	GACUUGUAGAGAAUCCUG	770	13845	GACUUGUAGAGAAUCCUG	770	13863	CAGGAUUCUUAUAGAAUUC	2421
13863	GACAUUAUACGGUUAUUG	771	13863	GACAUUAUACGGUUAUUG	771	13881	CAUUAACGCGUAAAGUAGUC	2422
13881	GUUAUUAUUGGAGGUG	772	13881	GUUAUUAUUGGAGGUG	772	13899	CAGCUCACCCUAAAGUAGC	2423
13899	GUACGCCAAUUAUUAUUA	773	13899	GUACGCCAAUUAUUAUUA	773	13917	UUAAUUAUUAUUGGCGUAC	2424
13917	AAGACUGUACAAUUCUGCG	774	13917	AAGACUGUACAAUUCUGCG	774	13935	CGCAGAAUUGUAGAGUUCU	2425
13935	GAUGCUAUGCGUGAUGCAG	775	13935	GAUGCUAUGCGUGAUGCAG	775	13953	CUGCAUCACGCAUAGCAUC	2426
13953	GGCAUUGUAGGCGUACUGA	776	13953	GGCAUUGUAGGCGUACUGA	776	13971	UCAGUACGCCUACAAUGCC	2427
13971	ACAUUAGAUUAUACAGGAC	777	13971	ACAUUAGAUUAUACAGGAC	777	13989	GAUCCUGAUUAUUAUUAU	2428
13989	CUUAUUGGAAUUGGUACG	778	13989	CUUAUUGGAAUUGGUACG	778	14007	CGUACCAUUAUUAUUAAG	2429
14007	GAUUCGGUGAUUUCGUAC	779	14007	GAUUCGGUGAUUUCGUAC	779	14025	GUACGAAUUAUUAUUAU	2430
14025	CAAGUAGCACCAGGCGCG	780	14025	CAAGUAGCACCAGGCGCG	780	14043	CGCAGCCUGGUGUACUUG	2431
14043	GGAGUUCUUAUUGGUAU	781	14043	GGAGUUCUUAUUGGUAU	781	14061	AUCCACAUAUAGGAACUCC	2432
14061	UCAUUAUUAUUAUUGCUGA	782	14061	UCAUUAUUAUUAUUGCUGA	782	14079	UCAGCAUUAUUAUUAUUA	2433
14079	AUGCCCAUCCUUAUUAUUA	783	14079	AUGCCCAUCCUUAUUAUUA	783	14097	UCAAGUGAGGAGUUGGCAU	2434
14097	ACUAGGGCAUUGGCGUG	784	14097	ACUAGGGCAUUGGCGUG	784	14115	CAGCAGCCAAUUGCCUAGU	2435
14115	GAGUCCCAUUAUUGGUGCUG	785	14115	GAGUCCCAUUAUUGGUGCUG	785	14133	CAGCAUCCAAUUAUUGGACUC	2436
14133	GAUCUGCAAAACCAUUA	786	14133	GAUCUGCAAAACCAUUA	786	14151	UAAGUGGUUUAUUGGAGUAC	2437
14151	AUUAAGUGGGAUUAUUGCUGA	787	14151	AUUAAGUGGGAUUAUUGCUGA	787	14169	UCAGCAAAUUAUUAUUAU	2438
14169	AAUUAUUAUUAUUAUUAUUA	788	14169	AAUUAUUAUUAUUAUUAUUA	788	14187	CUUCCGUAAUUAUUAUUAU	2439
14187	GAGAGCAUUAUUAUUAUUAU	789	14187	GAGAGCAUUAUUAUUAUUAU	789	14205	CGAAGAGACAAGUUCUCUC	2440
14205	GACCGUUAUUAUUAUUAUUA	790	14205	GACCGUUAUUAUUAUUAUUA	790	14223	AAUUAUUAUUAUUAUUAUUA	2441
14223	UGGAGCAGACAUUAUUAUUA	791	14223	UGGAGCAGACAUUAUUAUUA	791	14241	GAUGUUAUUAUUAUUAUUA	2442
14241	CCCAUUAUUAUUAUUAUUAU	792	14241	CCCAUUAUUAUUAUUAUUAU	792	14259	AACAGUUAUUAUUAUUAUUA	2443

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14259	UUGGAUGAUGGUGUAUCC	793	14259	UUGGAUGAUGGUGUAUCC	793	14277	GGAUACACCUAUAUCCAA	2444
14277	CUUCAUUGGCAACAUUA	794	14277	CUUCAUUGGCAACAUUA	794	14295	UAAAGUUUGCACAUAAG	2445
14295	AAUGGUUAUUUUCUACUG	795	14295	AAUGGUUAUUUUCUACUG	795	14313	CAGUAGAAUAACACAUU	2446
14313	GUGUUUCCACCUACAAGU	796	14313	GUGUUUCCACCUACAAGU	796	14331	AACUUGAUGGUGAAACAC	2447
14331	UUUGGACCAUUAAGAA	797	14331	UUUGGACCAUUAAGAA	797	14349	UUUUAUAGUGGUCCAAA	2448
14349	AAAUUUUUGUAUGGUG	798	14349	AAAUUUUUGUAUGGUG	798	14367	CACCAUCUACAAUAUUU	2449
14367	GUUCCUUUUGUUUCAA	799	14367	GUUCCUUUUGUUUCAA	799	14385	UAGAAACAAAGGAAAC	2450
14385	ACUGGAUACCAUUUCGUG	800	14385	ACUGGAUACCAUUUCGUG	800	14403	CACAAAAGGUUCCAGU	2451
14403	GAGUAGGAGUGUAUAUA	801	14403	GAGUAGGAGUGUAUAUA	801	14421	UAUGAACGACUCCUAACUC	2452
14421	AAUCAGGAUGUAACUUAAC	802	14421	AAUCAGGAUGUAACUUAAC	802	14439	GUAAGUUUAUUAUCCUGAUU	2453
14439	CAUAGCUCGUGUCAGU	803	14439	CAUAGCUCGUGUCAGU	803	14457	AACUGAGACGCGAGCUAUG	2454
14457	UUCAAGGAACUUUAAGUGU	804	14457	UUCAAGGAACUUUAAGUGU	804	14475	ACACUAAAAGUCCUUGAA	2455
14475	UAUGCUGGUAUCCAGCUA	805	14475	UAUGCUGGUAUCCAGCUA	805	14493	UAGCUGGUAUCCAGCUA	2456
14493	AUGCAUGCAGCUUUGGCA	806	14493	AUGCAUGCAGCUUUGGCA	806	14511	UGCCAGAAAGCUAUGCAU	2457
14511	AAUUUAUUGCUAUAUAAC	807	14511	AAUUUAUUGCUAUAUAAC	807	14529	GUUUUAUUAAGCAUUAUU	2458
14529	CGCACUAUAGCUUUAUAC	808	14529	CGCACUAUAGCUUUAUAC	808	14547	CUGAAAAGCAUUAUGGCG	2459
14547	GUAGCUGCAUAACAAACA	809	14547	GUAGCUGCAUAACAAACA	809	14565	UGUUUUAUUAUGGCGUAC	2460
14565	AAUGUUGCUUUAACAAACUG	810	14565	AAUGUUGCUUUAACAAACUG	810	14583	CAGUUUAAAAGCAACAUU	2461
14583	GUCAAACCGGUAAUUUA	811	14583	GUCAAACCGGUAAUUUA	811	14601	UAAAUAUACCGGUUUGAC	2462
14601	AAUAAAGACUUAUUAUGACU	812	14601	AAUAAAGACUUAUUAUGACU	812	14619	AGCUAAAAGCUCUUUAUU	2463
14619	UUUGCUGGUCUAAAGGUU	813	14619	UUUGCUGGUCUAAAGGUU	813	14637	AGCUUUAAGCACACAGAA	2464
14637	UUCUUUAAGGAAGGAAGU	814	14637	UUCUUUAAGGAAGGAAGU	814	14655	AACUUUCCUUAUUAAGAA	2465
14655	UCUGUUUAACUAAACACU	815	14655	UCUGUUUAACUAAACACU	815	14673	AGUUUUUAUUAUUAACAGA	2466
14673	UUCUUUUUUGCUCAGGUG	816	14673	UUCUUUUUUGCUCAGGUG	816	14691	CAUCUGAGCAAGGAAGAA	2467
14691	GGCAACGCGUAUACAGUG	817	14691	GGCAACGCGUAUACAGUG	817	14709	CACUGUAAGCAGGUUGCC	2468
14709	GAUUAUGACUUAUUAUGGU	818	14709	GAUUAUGACUUAUUAUGGU	818	14727	AACGAUUAUUAUUAUUAU	2469
14727	UAUUAUCUGCCAAACAUU	819	14727	UAUUAUCUGCCAAACAUU	819	14745	ACAUUUUGGCGAGUAUAU	2470
14745	UGUGUAUACAGACACUCC	820	14745	UGUGUAUACAGACACUCC	820	14763	GGAGUUGUCUGUAUUAACA	2471
14763	CUAUUCGUAGUUAAGUUG	821	14763	CUAUUCGUAGUUAAGUUG	821	14781	CAACUUAACUACGAAUAG	2472
14781	GUUGAUAUUAUUAUUAU	822	14781	GUUGAUAUUAUUAUUAU	822	14799	AAUCAAAGUAUUAUUAACA	2473
14799	UGUUAUGGUGGUGGUGUA	823	14799	UGUUAUGGUGGUGGUGUA	823	14817	UACAGCCCAUUAUUAACA	2474
14817	AUUAUUGCCAAACAAAGUA	824	14817	AUUAUUGCCAAACAAAGUA	824	14835	UUUAUUUGGUGGUAUUAU	2475
14835	AUGGUUAACAUUAUUAU	825	14835	AUGGUUAACAUUAUUAU	825	14853	UAUCCAGAUUAUUAUUAU	2476
14853	AAUUCAGCUGGUUUCUUAU	826	14853	AAUUCAGCUGGUUUCUUAU	826	14871	AUGGAAACCAUUAUUAU	2477
14871	UUUAUUAUUAUUAUUAU	827	14871	UUUAUUAUUAUUAUUAU	827	14889	CGUUAUUAUUAUUAUUAU	2478
14889	GUUAGACUUAUUAUUAU	828	14889	GUUAGACUUAUUAUUAU	828	14907	AGUUAUUAUUAUUAUUAU	2479
14907	UCAUAGGUAUUAUUAUUAU	829	14907	UCAUAGGUAUUAUUAUUAU	829	14925	GAUCCUUAUUAUUAUUAU	2480
14925	CAAGUAGCUCUUAUUAUUAU	830	14925	CAAGUAGCUCUUAUUAUUAU	830	14943	ACGCGAAAGGUGCAUUAU	2481
14943	UAUUAUUAUUAUUAUUAU	831	14943	UAUUAUUAUUAUUAUUAU	831	14961	UUAUUAUUAUUAUUAUUAU	2482
14961	AUCCUUAUUAUUAUUAUUAU	832	14961	AUCCUUAUUAUUAUUAUUAU	832	14979	UUAUUAUUAUUAUUAUUAU	2483
14979	AUGAAUUAUUAUUAUUAUUAU	833	14979	AUGAAUUAUUAUUAUUAUUAU	833	14997	UGGCAUUAUUAUUAUUAUUAU	2484
14997	AUUAUGCAAAAGUAUUAUUAU	834	14997	AUUAUGCAAAAGUAUUAUUAU	834	15015	CUCUAUUAUUAUUAUUAUUAU	2485

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15015	GCUCGACCGUAGCUGGUG	835	15015	GCUCGACCGUAGCUGGUG	835	15033	CACCAGCJACGGUGCGAGC	2486
15033	GUCUCUACUCUGUAGUACUA	836	15033	GUCUCUACUCUGUAGUACUA	836	15051	UAGUACUACAGAUAGAGAC	2487
15051	AUGACAAUAGACAGUUC	837	15051	AUGACAAUAGACAGUUC	837	15069	GAACUGUCUUAUUGUACU	2488
15069	CAUCAGAAUUAUUGAAGU	838	15069	CAUCAGAAUUAUUGAAGU	838	15087	ACUCAAUUAUUGUACU	2489
15087	UCAUAGCCGCCACUAGAG	839	15087	UCAUAGCCGCCACUAGAG	839	15105	CUCUAGUGCGGCUUAUGA	2490
15105	GGAGCUACUGUGGUAAUUG	840	15105	GGAGCUACUGUGGUAAUUG	840	15123	CAUUAACCAAGUAGUCC	2491
15123	GGAACAAGCAUUAUUG	841	15123	GGAACAAGCAUUAUUG	841	15141	CGUAAACUUGCUUUGUCC	2492
15141	GGUGGUGGCAUUAUUG	842	15141	GGUGGUGGCAUUAUUG	842	15159	ACAUUAUUGCCAGCCACC	2493
15159	UUAAAACUGUUAACAGUG	843	15159	UUAAAACUGUUAACAGUG	843	15177	CACUGUAAACAGUUUUUAA	2494
15177	GAUGUAGAAACUCCACACC	844	15177	GAUGUAGAAACUCCACACC	844	15195	GGUGGAGUUUCUACAU	2495
15195	CUUAUGGUGGGAUUAUC	845	15195	CUUAUGGUGGGAUUAUC	845	15213	GAUAAUCCCAACCCAUAG	2496
15213	CCAAAUGUGAGAGAGCCA	846	15213	CCAAAUGUGAGAGAGCCA	846	15231	UGGCUUGUCACAUUUUGG	2497
15231	AUGCUAAACUGCUUAGGA	847	15231	AUGCUAAACUGCUUAGGA	847	15249	UCCUAGCAUUAUAGGCAU	2498
15249	AUAUAGCCUCUUGUUC	848	15249	AUAUAGCCUCUUGUUC	848	15267	GAACAAGAGAGGCCAUUAU	2499
15267	CUUGCUCGCAACAUAACA	849	15267	CUUGCUCGCAACAUAACA	849	15285	UGUUAUUGUUGCGAGCAAG	2500
15285	ACUUGCUUAACUUAUCAC	850	15285	ACUUGCUUAACUUAUCAC	850	15303	GUGUAAUUAACAGCAAGU	2501
15303	CACCGUUCUACAGGUUAG	851	15303	CACCGUUCUACAGGUUAG	851	15321	CUAACCUUGUAGAACCGUG	2502
15321	GCUAACGAGUGCGGCAAG	852	15321	GCUAACGAGUGCGGCAAG	852	15339	CUUGCGCACACUGUUAAG	2503
15339	GUUAUAGUGAGAGUGUCA	853	15339	GUUAUAGUGAGAGUGUCA	853	15357	UGACCAUCACUUAUUAUC	2504
15357	AUGUGGCGGCUACUUAU	854	15357	AUGUGGCGGCUACUUAU	854	15375	UAUAGCAUUAAGCAGUUGU	2505
15375	UAUUAUAAACAGGUGGAA	855	15375	UAUUAUAAACAGGUGGAA	855	15393	UUAUAGCAUUAAGCAGUUGU	2506
15393	ACAUAUCCGUGAUGCUA	856	15393	ACAUAUCCGUGAUGCUA	856	15411	UAGCAUCCCGGAGUAGU	2507
15411	ACAACUGCUUAUGCUAAUA	857	15411	ACAACUGCUUAUGCUAAUA	857	15429	UAUAGCAUUAAGCAGUUGU	2508
15429	AGUGCUUUAACAUUUGUC	858	15429	AGUGCUUUAACAUUUGUC	858	15447	GACAAUUGUUAAGACACU	2509
15447	CAAGCUUUAACAGCCAAUG	859	15447	CAAGCUUUAACAGCCAAUG	859	15465	CAUUGCGUGUAAACAGCUUG	2510
15465	GUAAUAGCAUUCUUAACA	860	15465	GUAAUAGCAUUCUUAACA	860	15483	UUGAAAGAGUGCAUUAAC	2511
15483	ACUGAUGUUAUAGAUAG	861	15483	ACUGAUGUUAUAGAUAG	861	15501	CUAUCUUAUUAACCAUAGU	2512
15501	GCUGACAAGUAGUCCGCA	862	15501	GCUGACAAGUAGUCCGCA	862	15519	UGCGGACAUUAGUAGCAGC	2513
15519	AUUCUACACAGGCUUCU	863	15519	AUUCUACACAGGCUUCU	863	15537	AGAGCCUGUGUAGUAGU	2514
15537	UAUGAGUGUCUUAUAGAA	864	15537	UAUGAGUGUCUUAUAGAA	864	15555	UUCUUAAGAGACACUUA	2515
15555	AAUAGGGAUGUAGUUAUC	865	15555	AAUAGGGAUGUAGUUAUC	865	15573	CAUGAUAACAUCUCCUUAU	2516
15573	GAUUCGUGGAGUUAUUAU	866	15573	GAUUCGUGGAGUUAUUAU	866	15591	AAACUUAUUAACCAUUAUC	2517
15591	UACGCUUUAACGCUAAAC	867	15591	UACGCUUUAACGCUAAAC	867	15609	GUUUAACGAGGUAAGCGUA	2518
15609	CAUUCUCCAUAGAUUAUC	868	15609	CAUUCUCCAUAGAUUAUC	868	15627	GAUUAUUAUUAAGAAUAG	2519
15627	CUUUCUGAUGAGUCCGUUG	869	15627	CUUUCUGAUGAGUCCGUUG	869	15645	CAACGGCAUUAUAGAAAG	2520
15645	GUGUGCUUAUACAGUUAUC	870	15645	GUGUGCUUAUACAGUUAUC	870	15663	AGUUAUUAUUAAGCACAC	2521
15663	UAUGCGGCUCAAGGUUAAG	871	15663	UAUGCGGCUCAAGGUUAAG	871	15681	CUAAACCUUAGCGGCAUA	2522
15681	GUAGUAGCAUUAAGAAUC	872	15681	GUAGUAGCAUUAAGAAUC	872	15699	AGUUCUUAUUAUAGCUAC	2523
15699	UUUAAGGCAUUAUUAUUAU	873	15699	UUUAAGGCAUUAUUAUUAU	873	15717	UAUAAAGAACUUGCCUUAU	2524
15717	UAUCAAUUAUUAUUAUUAU	874	15717	UAUCAAUUAUUAUUAUUAU	874	15735	UGAACACAUUAUUAUUAU	2525
15735	AUGUCUGAGGCAAAUUAU	875	15735	AUGUCUGAGGCAAAUUAU	875	15753	AACAUAUUAUUAUUAUUAU	2526
15753	UGGACUGAGACUGACCUUA	876	15753	UGGACUGAGACUGACCUUA	876	15771	UAAGGUCAGUCUCAGUCCA	2527

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15771	ACUAAAGGACCUCACGAU	877	15771	ACUAAAGGACCUCACGAU	877	15789	AUUCGUGAGGUCUUAUAGU	2528
15789	UUUUGCUCACAGCAUCAA	878	15789	UUUUGCUCACAGCAUCAA	878	15807	UUGUAUGUGUGAGCAAAA	2529
15807	AUGCUAGUUAACAAGGAG	879	15807	AUGCUAGUUAACAAGGAG	879	15825	CUCCUUGUUAACUAGCAU	2530
15825	GAUGAUUACGUGUACCGC	880	15825	GAUGAUUACGUGUACCGC	880	15843	GCAGGUAACGUAUACUAC	2531
15843	CCUACCCAGAUCCAUCAA	881	15843	CCUACCCAGAUCCAUCAA	881	15861	UUGAUGGAUCUGGGUAAGG	2532
15861	AGAAUUAUAGGCGAGGCU	882	15861	AGAAUUAUAGGCGAGGCU	882	15879	AGCUGCGCCUUAUUAUCU	2533
15879	UGUUUUGCGAUAUUAUG	883	15879	UGUUUUGCGAUAUUAUG	883	15897	CAUAUACUACGCAAAAACA	2534
15897	GUCAAAACAGUAGUACAC	884	15897	GUCAAAACAGUAGUACAC	884	15915	GUGUACCAUCUGUUUUGAC	2535
15915	CUUAUGAUUAAAGGUUGG	885	15915	CUUAUGAUUAAAGGUUGG	885	15933	CGAACCUUUAUUAUUAAG	2536
15933	GUGUACUGGCUUAUUAUG	886	15933	GUGUACUGGCUUAUUAUG	886	15951	CAUCAUAGCCAGUGACAC	2537
15951	GCUUACCCACUUAACAAAC	887	15951	GCUUACCCACUUAACAAAC	887	15969	GUUUUGUAAGUGGGUAAGC	2538
15969	CAUCCUUAUCAGGAGUAUG	888	15969	CAUCCUUAUCAGGAGUAUG	888	15987	CAUACUCCUGAUUAGGAUG	2539
15987	GCUGAUGUCUUUACUUGU	889	15987	GCUGAUGUCUUUACUUGU	889	16005	ACAAGUGAAAGACAUACGC	2540
16005	UAUUUACAUAUUAUAGAA	890	16005	UAUUUACAUAUUAUAGAA	890	16023	UUCUAUUGUAUUGUAUUA	2541
16023	AAGUUACAUAUGAGCUUA	891	16023	AAGUUACAUAUGAGCUUA	891	16041	UAGCUCUAUUGUAUACUU	2542
16041	ACUGGCCACAUUGGAGCA	892	16041	ACUGGCCACAUUGGAGCA	892	16059	UUGCCAACAUUGGGCCAGU	2543
16059	AUGUAUCCGUAUUGCUAA	893	16059	AUGUAUCCGUAUUGCUAA	893	16077	UUAAGCAUUAACGGAUACAU	2544
16077	ACUAUAGUAACACCCUCAC	894	16077	ACUAUAGUAACACCCUCAC	894	16095	GUGAGGUGUUUAUUAUAGU	2545
16095	CGGUACUGGGAACCGAGU	895	16095	CGGUACUGGGAACCGAGU	895	16113	ACUCAGGUUCCAGUAACCG	2546
16113	UUUUUAGGCUUAUUAUACA	896	16113	UUUUUAGGCUUAUUAUACA	896	16131	UGUAACAUGCCUUAUAAAA	2547
16131	ACACCACUAUACUGUUGC	897	16131	ACACCACUAUACUGUUGC	897	16149	GCAAGACUGUAUUGGGUGU	2548
16149	CAGGCUUAGGUGUUGUG	898	16149	CAGGCUUAGGUGUUGUG	898	16167	CACAAGCACCUAACAGCCUG	2549
16167	GUUUUGGCAUUAUCACAGA	899	16167	GUUUUGGCAUUAUCACAGA	899	16185	UCUGUGAUUUGCACAUAUC	2550
16185	ACUUCACUUCGUUGCGGUG	900	16185	ACUUCACUUCGUUGCGGUG	900	16203	CACCGCAACGAAUGAAGU	2551
16203	GCCUGUAUAGGAGACCAU	901	16203	GCCUGUAUAGGAGACCAU	901	16221	AUGGUCUCCUAUUAACAGGC	2552
16221	UUCUAUGUUGCAAGUGCU	902	16221	UUCUAUGUUGCAAGUGCU	902	16239	AGCACUUGCAACAUAGGAA	2553
16239	UGCUAUGACCAUUGUAUUA	903	16239	UGCUAUGACCAUUGUAUUA	903	16257	AAUUGACAUGGUAUAGCA	2554
16257	UCAACAUCACACAAUUAU	904	16257	UCAACAUCACACAAUUAU	904	16275	CUAAUUUGUGUGAUGUUA	2555
16275	GUGUUGUCUGUUAUCCCU	905	16275	GUGUUGUCUGUUAUCCCU	905	16293	AGGGAUUAACAGACAACAC	2556
16293	UAUGUUUGCAUUGCCAG	906	16293	UAUGUUUGCAUUGCCAG	906	16311	CUGGGGCAUUGCAAAACAU	2557
16311	GGUUGUGAUGUCACUGAUG	907	16311	GGUUGUGAUGUCACUGAUG	907	16329	CAUCAGUGACAUACAACCC	2558
16329	GUGACACAUCUGUAUUAU	908	16329	GUGACACAUCUGUAUUAU	908	16347	CUAGUAACAGUUGUUCAC	2559
16347	GGAGGUUAGGCUUAUUAU	909	16347	GGAGGUUAGGCUUAUUAU	909	16365	AAUUAUAGCUCAUACCUCC	2560
16365	UGCAAGUCACAUAAAGCCUC	910	16365	UGCAAGUCACAUAAAGCCUC	910	16383	GAGGCUUAUGUGACUUGCA	2561
16383	CCCAUUAUUAUUAUUAUUA	911	16383	CCCAUUAUUAUUAUUAUUA	911	16401	AUAUUGGAAACUAUAGGG	2562
16401	UGUGCUAAUGGUCAGGUUU	912	16401	UGUGCUAAUGGUCAGGUUU	912	16419	AAACCGACCAUUAAGCACA	2563
16419	UUUGGUUUAUACAAAACA	913	16419	UUUGGUUUAUACAAAACA	913	16437	UGUUUUUUAUUAUAAACAAA	2564
16437	ACAUGUGUAGGCAUGACACA	914	16437	ACAUGUGUAGGCAUGACACA	914	16455	UGUCACUGCCUACACAUUGU	2565
16455	AAUGUCACUGACUUAUUAUG	915	16455	AAUGUCACUGACUUAUUAUG	915	16473	CAUUAAGUCAGUGACAUU	2566
16473	GCGAUGCAACAUUGUAUUA	916	16473	GCGAUGCAACAUUGUAUUA	916	16491	AAUCACAUGUUGCUAUCGC	2567
16491	UGGACUUAUUGCGGCAUUA	917	16491	UGGACUUAUUGCGGCAUUA	917	16509	AAUCGCCAGCAUUAUGUCCA	2568
16509	UACAUACUUGGCAACACUU	918	16509	UACAUACUUGGCAACACUU	918	16527	AAGUGUUGGCAAGUAUGUA	2569

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16527	UGUACUGAGAGACUACGC	919	16527	UGUACUGAGAGACUACGC	919	16545	GCUUGAGUCUCUCAGUACA	2570
16545	CUUUUCGCGAGAGAAACGC	920	16545	CUUUUCGCGAGAGAAACGC	920	16563	GCGUUUCUGCUGCGAAAG	2571
16563	CUCAAAGCCACUGAGGAAA	921	16563	CUCAAAGCCACUGAGGAAA	921	16581	UUCCUCAGUGGCUUUAG	2572
16581	ACAUUUAAGCUGCAUAG	922	16581	ACAUUUAAGCUGCAUAG	922	16599	CAUUGACAGCUUAAUUG	2573
16599	GGUUAUAGCUGUACGCG	923	16599	GGUUAUAGCUGUACGCG	923	16617	CGUGUACAGUGGCAUACC	2574
16617	GGAUGACUCUGACAGAG	924	16617	GGAUGACUCUGACAGAG	924	16635	CUCUGACAGAGUACUUC	2575
16635	GAUUGCAUUCUUAUGGG	925	16635	GAUUGCAUUCUUAUGGG	925	16653	CUCUGAAGAGUACUUC	2576
16653	GAGGUUGGAAACCUAGAC	926	16653	GAGGUUGGAAACCUAGAC	926	16671	GUCUAGGUUUUCCAAACCUC	2577
16671	CCACCAUUGAACAGAAACU	927	16671	CCACCAUUGAACAGAAACU	927	16689	AGUUCUGUUAUUGGUGG	2578
16689	UAUGUCUUAUUGUUAACC	928	16689	UAUGUCUUAUUGUUAACC	928	16707	GGUACCAUUAAGACACA	2579
16707	CGUGUUAUUAUUAUAGUA	929	16707	CGUGUUAUUAUUAUAGUA	929	16725	ACUUAUUAUUAUUAUAG	2580
16725	AAAGUACAGUUGGAGAGU	930	16725	AAAGUACAGUUGGAGAGU	930	16743	ACUCUCAAUCUGUACUUC	2581
16743	UACACCUUUGAAUAAAGGUG	931	16743	UACACCUUUGAAUAAAGGUG	931	16761	CACCUUUUUAUUAAGGUGA	2582
16761	GACUUAUGGAGUAGUUG	932	16761	GACUUAUGGAGUAGUUG	932	16779	CAACAGUACACCAUAGUC	2583
16779	GUGUACAGAGGUACUACGA	933	16779	GUGUACAGAGGUACUACGA	933	16797	UCGUAUACCUUUGUACAC	2584
16797	ACAUACAAGUUAUUGUUG	934	16797	ACAUACAAGUUAUUGUUG	934	16815	UAGAAUUAUUAUUAUAG	2585
16815	GGUGAUUAUUAUUGUUGA	935	16815	GGUGAUUAUUAUUGUUGA	935	16833	UACAACAAGUUAUUAUAG	2586
16833	ACAUCUACACUGUUAUUGC	936	16833	ACAUCUACACUGUUAUUGC	936	16851	GCAUUAUUAUUAUUAUAG	2587
16851	CCACUUAUUAUUAUUAUAG	937	16851	CCACUUAUUAUUAUUAUAG	937	16869	GAGUAGGUGUUAUUAUAG	2588
16869	CUAGUGCACAAGAGCAGU	938	16869	CUAGUGCACAAGAGCAGU	938	16887	AGUGCUUUAUUAUUAUAG	2589
16887	UAUGUAGAAUUAUUAUAG	939	16887	UAUGUAGAAUUAUUAUAG	939	16905	AGCAUUAUUAUUAUUAUAG	2590
16905	UUGUACCAACACUACACA	940	16905	UUGUACCAACACUACACA	940	16923	UGUUAUUAUUAUUAUUAUAG	2591
16923	AUCUACAGUAGUUAUUAU	941	16923	AUCUACAGUAGUUAUUAU	941	16941	UAGAAUUAUUAUUAUUAUAG	2592
16941	AGCAUUAUUAUUAUUAUAG	942	16941	AGCAUUAUUAUUAUUAUAG	942	16959	GAUUAUUAUUAUUAUUAUAG	2593
16959	CAAAAGGUGGCAUUAUUAU	943	16959	CAAAAGGUGGCAUUAUUAU	943	16977	UUUGCAUUAUUAUUAUUAUAG	2594
16977	AAGUACUUAUUAUUAUUAU	944	16977	AAGUACUUAUUAUUAUUAU	944	16995	CUUGGAGUUAUUAUUAUUAUAG	2595
16995	GGACACCUUUAUUAUUAUAG	945	16995	GGACACCUUUAUUAUUAUAG	945	17013	UACCAUUAUUAUUAUUAUAG	2596
17013	AAGAGUUAUUAUUAUUAUAG	946	17013	AAGAGUUAUUAUUAUUAUAG	946	17031	CGUUAUUAUUAUUAUUAUAG	2597
17031	GGACUUGCUCUUAUUAUAG	947	17031	GGACUUGCUCUUAUUAUAG	947	17049	GGUUAUUAUUAUUAUUAUAG	2598
17049	CCAUUGCUCUUAUUAUUAUAG	948	17049	CCAUUGCUCUUAUUAUUAUAG	948	17067	ACAUUAUUAUUAUUAUUAUAG	2599
17067	UAUACGGCAUUAUUAUUAUAG	949	17067	UAUACGGCAUUAUUAUUAUAG	949	17085	CAUGAGCAUUAUUAUUAUAG	2600
17085	GCAGCUGUUAUUAUUAUUAUAG	950	17085	GCAGCUGUUAUUAUUAUUAUAG	950	17103	AUAGGCAUUAUUAUUAUAG	2601
17103	UGUAAAAGGCAUUAUUAUAG	951	17103	UGUAAAAGGCAUUAUUAUAG	951	17121	AUUUAUUAUUAUUAUUAUAG	2602
17121	UAUUUGCCCAUUAUUAUUAUAG	952	17121	UAUUUGCCCAUUAUUAUUAUAG	952	17139	AUUUAUUAUUAUUAUUAUAG	2603
17139	UGUUAUUAUUAUUAUUAUAG	953	17139	UGUUAUUAUUAUUAUUAUAG	953	17157	CAGGUUAUUAUUAUUAUUAUAG	2604
17157	GCGUGGCGCGUUAUUAUUAUAG	954	17157	GCGUGGCGCGUUAUUAUUAUAG	954	17175	ACUUAUUAUUAUUAUUAUAG	2605
17175	UGUUUAUUAUUAUUAUUAUAG	955	17175	UGUUUAUUAUUAUUAUUAUAG	955	17193	CUUUAUUAUUAUUAUUAUAG	2606
17193	GUGAAUUAUUAUUAUUAUUAUAG	956	17193	GUGAAUUAUUAUUAUUAUUAUAG	956	17211	GUUUAUUAUUAUUAUUAUAG	2607
17211	CAGUUAUUAUUAUUAUUAUUAUAG	957	17211	CAGUUAUUAUUAUUAUUAUUAUAG	957	17229	GAGUUAUUAUUAUUAUUAUAG	2608
17229	GUAAUUAUUAUUAUUAUUAUUAUAG	958	17229	GUAAUUAUUAUUAUUAUUAUUAUAG	958	17247	UUUUAUUAUUAUUAUUAUUAUAG	2609
17247	ACAACUGCAUUAUUAUUAUUAUAG	959	17247	ACAACUGCAUUAUUAUUAUUAUAG	959	17265	CUAAUUAUUAUUAUUAUUAUAG	2610
17265	GUCUUAUUAUUAUUAUUAUUAUAG	960	17265	GUCUUAUUAUUAUUAUUAUUAUAG	960	17283	UAGAGUUAUUAUUAUUAUUAUAG	2611

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17283	AUGGCUACUAAUUAUGACU	961	17283	AUGGCUACUAAUUAUGACU	961	17301	AGUCAUAAUUAAGUAGCCAU	2612
17301	UUGAGUGUUGUCAAUAGCUA	962	17301	UUGAGUGUUGUCAAUAGCUA	962	17319	UAGCAUUAAGCAACACUAA	2613
17319	AGACUUCGUGCAAAACACU	963	17319	AGACUUCGUGCAAAACACU	963	17337	AGUGUUUUGCACGAAGCU	2614
17337	UACGUCUAAUUGGCGAUC	964	17337	UACGUCUAAUUGGCGAUC	964	17355	GAUCGCCAAUUAAGACGUA	2615
17355	CCUGCUCAAUUAACCGCC	965	17355	CCUGCUCAAUUAACCGCC	965	17373	GGCGUGUAAUUGAGCAGG	2616
17373	CCCGGCACUUGCGUACUA	966	17373	CCCGGCACUUGCGUACUA	966	17391	UAGUCAGCAUUGUGCGGG	2617
17391	AAAGGCACUAGAACCCAG	967	17391	AAAGGCACUAGAACCCAG	967	17409	CUGGUUCUAGUGUGCCUUA	2618
17409	GAUAUUUUAAUUCAGUGU	968	17409	GAUAUUUUAAUUCAGUGU	968	17427	ACACUGAAUUAUUUUUUC	2619
17427	UGCAGACUUAUGAAACAA	969	17427	UGCAGACUUAUGAAACAA	969	17445	UUGUUUUCAUAGUCUGCA	2620
17445	UAGGUCCAGACAUUUC	970	17445	UAGGUCCAGACAUUUC	970	17463	GGAAACUGUCUGGACCUAU	2621
17463	CUUGGAACUUGCGCGU	971	17463	CUUGGAACUUGCGCGU	971	17481	AAGCGGACAAUUCGCAAG	2622
17481	UGUGCGUGGAAUUGUUG	972	17481	UGUGCGUGGAAUUGUUG	972	17499	CAACAAUUUCAGCAGGACA	2623
17499	GACACUGAGUGCUUUAAG	973	17499	GACACUGAGUGCUUUAAG	973	17517	CUAAAGCACUCACAGUGUC	2624
17517	GUUAUGACAAUAGCUAA	974	17517	GUUAUGACAAUAGCUAA	974	17535	UAGCUUUAUUGUCAUAAAC	2625
17535	AAAGCACAAAGGAUAGU	975	17535	AAAGCACAAAGGAUAGU	975	17553	ACUUAUCCUUGUGUCUUA	2626
17553	UCAGCUCAAUGCUUCAA	976	17553	UCAGCUCAAUGCUUCAA	976	17571	UUUUAAGCAUUGAGCUGA	2627
17571	AUGUUUACAAAGGUGUA	977	17571	AUGUUUACAAAGGUGUA	977	17589	UAACACCUUUGUAGAACAU	2628
17589	AUACACAUAGUUAUUAU	978	17589	AUACACAUAGUUAUUAU	978	17607	AUGAAACAUCAGUGUAUUA	2629
17607	UCUGCAUUAACAGACCUC	979	17607	UCUGCAUUAACAGACCUC	979	17625	GAGGUCUGUUGAUUGCAGA	2630
17625	CAAAUAGGCGUUAAGAG	980	17625	CAAAUAGGCGUUAAGAG	980	17643	CUCUUAACAAGCCUUAUUG	2631
17643	GAUUUUCUUAACGCAUUC	981	17643	GAUUUUCUUAACGCAUUC	981	17661	GAUUGCGUGUAGAGAAUUC	2632
17661	CCUGCUUGGAGAAAGCUG	982	17661	CCUGCUUGGAGAAAGCUG	982	17679	CAGCUUUUCUCCAAAGCAGG	2633
17679	GUUUUAUCUCACCUUAUA	983	17679	GUUUUAUCUCACCUUAUA	983	17697	UAUAAGGUGAGAUAAAC	2634
17697	AAUUCACAGAACGUGUAG	984	17697	AAUUCACAGAACGUGUAG	984	17715	CUACAGCGUUCUGUGAAUUC	2635
17715	GCUUCAAAAUUCUAGGAU	985	17715	GCUUCAAAAUUCUAGGAU	985	17733	AUCCUAAGAUUUUUGAAGC	2636
17733	UUGCCUACGCAGACUGUUG	986	17733	UUGCCUACGCAGACUGUUG	986	17751	CAACAGUCUGCGUAGGCAA	2637
17751	GAUUAUCACAGGUGUUCUG	987	17751	GAUUAUCACAGGUGUUCUG	987	17769	CAGAACCCUGUGAUGAAUC	2638
17769	GAUAUGACUAUGUCAUAU	988	17769	GAUAUGACUAUGUCAUAU	988	17787	AUAUGACUAUGUCAUAUUC	2639
17787	UUCACACAAACUACUGAAA	989	17787	UUCACACAAACUACUGAAA	989	17805	UUUCAGUAGUUGUGUGAA	2640
17805	ACAGCACACUCUUGUAUUG	990	17805	ACAGCACACUCUUGUAUUG	990	17823	CAUUAACAAGAGUGUGUGU	2641
17823	GUCAACCGCUUCAAUGUGG	991	17823	GUCAACCGCUUCAAUGUGG	991	17841	CCACAUAAGAGCGGUUGAC	2642
17841	GCUAUCACAAGGCAAA	992	17841	GCUAUCACAAGGCAAA	992	17859	UUUUUGCCCUUGUGAUAGC	2643
17859	AUUGGCAUUUUGUGCAUAA	993	17859	AUUGGCAUUUUGUGCAUAA	993	17877	UAUUGCACAAAUUGCCAAU	2644
17877	AUGUCUGAUAAGAUUUAU	994	17877	AUGUCUGAUAAGAUUUAU	994	17895	AAAGAUUCUUAUCAGACAU	2645
17895	UAUGACAAACUGCAUUUA	995	17895	UAUGACAAACUGCAUUUA	995	17913	UAUUUUGCAGUUUGUCAUA	2646
17913	ACAAGUCUAGAAUACCCAC	996	17913	ACAAGUCUAGAAUACCCAC	996	17931	GUGGUUUUUAUAGACUUGU	2647
17931	CGUCGCAUUGGCUACAU	997	17931	CGUCGCAUUGGCUACAU	997	17949	AUGUAGCCACAUUGCGACG	2648
17949	UUAACAAGCAGAAAUUA	998	17949	UUAACAAGCAGAAAUUA	998	17967	UUAUAUUUUCUGCUUUGUA	2649
17967	ACUGGACUUUUUAAGGACU	999	17967	ACUGGACUUUUUAAGGACU	999	17985	AGUCCUUUAAAAGUCCAGU	2650
17985	UGUAGUAAGAUUAUACUG	1000	17985	UGUAGUAAGAUUAUACUG	1000	18003	CAGUUAUGAUUUUACUACA	2651
18003	GGUCUUAUCCUACACAGG	1001	18003	GGUCUUAUCCUACACAGG	1001	18021	CCUGUGAGGAGUAGACAC	2652
18021	GCACCUACACACCCUACGG	1002	18021	GCACCUACACACCCUACGG	1002	18039	CGCUGAGGUGUGUAGGUGC	2653

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18039	GUUGAUUAUAAAGUUAAGA	1003	18039	GUUGAUUAUAAAGUUAAGA	1003	18057	UCUUGAACUUUUAUAUACAAC	2654
18057	ACUGAAGGAUUAUGUUG	1004	18057	ACUGAAGGAUUAUGUUG	1004	18075	CAACACAUAAUCCUUCAGUC	2655
18075	GACUAACCGCAUACCAA	1005	18075	GACUAACCGCAUACCAA	1005	18093	UUGUAUCCUGGUUAUGUC	2656
18093	AAGGACUAGACCUACCGUA	1006	18093	AAGGACUAGACCUACCGUA	1006	18111	UACGGUAGGUCAUGUCCUU	2657
18111	AGACUACUCUAUGAGG	1007	18111	AGACUACUCUAUGAGG	1007	18129	CAUCAUAGAGUAGUGU	2658
18129	GGUUUAAAUAUAUACC	1008	18129	GGUUUAAAUAUAUACC	1008	18147	GGUAUAUAAUUUGAAACG	2659
18147	CAAGUACUAGGUUACCUA	1009	18147	CAAGUACUAGGUUACCUA	1009	18165	UAGGGUACCAUUGACUUG	2660
18165	AAUAUGUUUAUACCCGCG	1010	18165	AAUAUGUUUAUACCCGCG	1010	18183	CGCGGUAGUAAACAUUU	2661
18183	GAAGAAGCUAUUCGUCAG	1011	18183	GAAGAAGCUAUUCGUCAG	1011	18201	CGUGAGGAUAGCUUCUUC	2662
18201	GUUGUGUGGAGGUUGGCU	1012	18201	GUUGUGUGGAGGUUGGCU	1012	18219	AGCAAUCCACGCACGAAC	2663
18219	UUUGAUUAGAGGCGUGUC	1013	18219	UUUGAUUAGAGGCGUGUC	1013	18237	GACAGCCUUAUACAUAAC	2664
18237	CAUGAACUAGAGUGUG	1014	18237	CAUGAACUAGAGUGUG	1014	18255	CAGCAUCUAGUUGCAUG	2665
18255	GUGGUAUUAACCUACCUUC	1015	18255	GUGGUAUUAACCUACCUUC	1015	18273	GAGGUAGGUUAGUACCCAC	2666
18273	CUCAGCUAGGAUUUUA	1016	18273	CUCAGCUAGGAUUUUA	1016	18291	UAGAAAUCCUAGGUGGAG	2667
18291	ACAGGUUAUAUAUAUAUA	1017	18291	ACAGGUUAUAUAUAUAUA	1017	18309	CUACUAAGUAAACACCUUC	2668
18309	GCUGUACCGACUGGUUAUG	1018	18309	GCUGUACCGACUGGUUAUG	1018	18327	CUAACCCAGUCGGUACAGC	2669
18327	GUUGACACUGAAUAUAUA	1019	18327	GUUGACACUGAAUAUAUA	1019	18345	UGUUAUUUUCAGUGUACAC	2670
18345	ACAGAAUUAUACCAAGUA	1020	18345	ACAGAAUUAUACCAAGUA	1020	18363	UAACUCUGGUGAAUUCUGU	2671
18363	AUGAAAUUAUACCAAGUA	1021	18363	AUGAAAUUAUACCAAGUA	1021	18381	CUGGUGGAGGUUUUGCAUU	2672
18381	GUUGACCGCUUAUAUAUA	1022	18381	GUUGACCGCUUAUAUAUA	1022	18399	GAUGUUUAACUUGGUACAC	2673
18399	CUUAUACCAUUAUAUAUA	1023	18399	CUUAUACCAUUAUAUAUA	1023	18417	UAUACAUAGAGUGGUUAAG	2674
18417	AAAGGUUUGCCUUGGAUG	1024	18417	AAAGGUUUGCCUUGGAUG	1024	18435	CAUCCAGGCGAAGCCUUU	2675
18435	GUAGUGCGUAUUAAGUA	1025	18435	GUAGUGCGUAUUAAGUA	1025	18453	CUACUUAUAUACCGACUAC	2676
18453	GUACAAUUGCUACGUAUA	1026	18453	GUACAAUUGCUACGUAUA	1026	18471	UAUACUGAGCAUUUGUAC	2677
18471	ACACUGAAAGGAUUGUAC	1027	18471	ACACUGAAAGGAUUGUAC	1027	18489	CUGACAAUCCUUAUUGUAC	2678
18489	GACAGAGUGGUUUGUCC	1028	18489	GACAGAGUGGUUUGUCC	1028	18507	GGACGAACACGACUCUGUC	2679
18507	CUUUGGCGCAUGGCUUUG	1029	18507	CUUUGGCGCAUGGCUUUG	1029	18525	CAAGCCAUUGCCGCAAG	2680
18525	GAGCUUACAUUAUAUAUA	1030	18525	GAGCUUACAUUAUAUAUA	1030	18543	ACUUAUUGAUUAUAUAUA	2681
18543	UACUUAUUAUAUAUAUAUA	1031	18543	UACUUAUUAUAUAUAUAUA	1031	18561	GUCAUAUUAUAUAUAUAUA	2682
18561	CCUGAAAGAACGUGUUGUC	1032	18561	CCUGAAAGAACGUGUUGUC	1032	18579	GACAAACGCUUUAUAUAUA	2683
18579	CUGUGGACAAACGUGCAA	1033	18579	CUGUGGACAAACGUGCAA	1033	18597	UUGCACGUUUGUACACAG	2684
18597	ACUUGCUUUUUAUAUAUA	1034	18597	ACUUGCUUUUUAUAUAUA	1034	18615	AUGAAGUAAGAAACAAAGU	2685
18615	UCAGAUUAUAUAUAUAUA	1035	18615	UCAGAUUAUAUAUAUAUA	1035	18633	AGCAGGAUAAGUAUAUAUA	2686
18633	UGAAUUAUAUAUAUAUAUA	1036	18633	UGAAUUAUAUAUAUAUAUA	1036	18651	AACCCACAGAAUAUAUAUA	2687
18651	UUUGACUAUAUAUAUAUAUA	1037	18651	UUUGACUAUAUAUAUAUAUA	1037	18669	GGUUAUAGACAUUAUAUAUA	2688
18669	CCAUUAUAUAUAUAUAUAUA	1038	18669	CCAUUAUAUAUAUAUAUAUA	1038	18687	GAACAUUAUAUAUAUAUAUA	2689
18687	CAGCAUUAUAUAUAUAUAUA	1039	18687	CAGCAUUAUAUAUAUAUAUA	1039	18705	CGUUAAGCCGCAUAUAUAUA	2690
18705	GUUAACCUUAUAUAUAUAUA	1040	18705	GUUAACCUUAUAUAUAUAUA	1040	18723	GGUUAUUAUAUAUAUAUAUA	2691
18723	CAUGAACCAUAUAUAUAUAUA	1041	18723	CAUGAACCAUAUAUAUAUAUA	1041	18741	CGUGCAUUAUAUAUAUAUAUA	2692
18741	GUUAACCUUAUAUAUAUAUAUA	1042	18741	GUUAACCUUAUAUAUAUAUAUA	1042	18759	CAUGCAUUAUAUAUAUAUAUA	2693
18759	GUGGCUUAUAUAUAUAUAUAUA	1043	18759	GUGGCUUAUAUAUAUAUAUAUA	1043	18777	UAGCAUUAUAUAUAUAUAUAUA	2694
18777	AUCAUGACUAUAUAUAUAUAUAUA	1044	18777	AUCAUGACUAUAUAUAUAUAUAUA	1044	18795	CUAAACAUUAUAUAUAUAUAUAUA	2695

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18795	GCAGUCCAUAGAGUGCUUUG	1045	18795	GCAGUCCAUAGAGUGCUUUG	1045	18813	CAAAGCACUACUAGGACUUC	2696
18813	GUUAAAGCGGUUUAUUGGU	1046	18813	GUUAAAGCGGUUUAUUGGU	1046	18831	ACCAUACCAAGCGUUAAC	2697
18831	UCUGUUAUUAACCUUAUA	1047	18831	UCUGUUAUUAACCUUAUA	1047	18849	UAAUAGGGUUAUUAACAGA	2698
18849	AUAGGAGUAUUAACCUUA	1048	18849	AUAGGAGUAUUAACCUUA	1048	18867	CCUCAGUUAUUAUUAUUA	2699
18867	GUUAAUUCUGUUGCAGAA	1049	18867	GUUAAUUCUGUUGCAGAA	1049	18885	UUCUGCAAGCAGAAUUAAC	2700
18885	AAAGUACAACACAUUGGUU	1050	18885	AAAGUACAACACAUUGGUU	1050	18903	CAAGCAUGUGUUGUUAUUA	2701
18903	GUGAUGUGCAUUGCUUG	1051	18903	GUGAUGUGCAUUGCUUG	1051	18921	CAAGCAUGUGUUGUUAUUA	2702
18921	GCUGAUAAGUUAUCCAGUUC	1052	18921	GCUGAUAAGUUAUCCAGUUC	1052	18939	GAACUGGAAACUUAUUAAC	2703
18939	CUUACUGACAUUGGAAUUC	1053	18939	CUUACUGACAUUGGAAUUC	1053	18957	GAUUAUCCAUUGUUAUUAAC	2704
18957	CCAAAGGCUUAUUAUUAUUA	1054	18957	CCAAAGGCUUAUUAUUAUUA	1054	18975	CACACUUGAUUAGCCUUAUUA	2705
18975	GUGCCUCAGGCUUAUUAUUA	1055	18975	GUGCCUCAGGCUUAUUAUUA	1055	18993	CUACUUAUAGCCUUAUUAUUA	2706
18993	GAUUGAAGUUAUUAUUAUUA	1056	18993	GAUUGAAGUUAUUAUUAUUA	1056	19011	CAUCGUAGAAUUAUUAUUA	2707
19011	GCUCAGCCAUUAUUAUUAUUA	1057	19011	GCUCAGCCAUUAUUAUUAUUA	1057	19029	UGUCACUACAUUGGCUUAUUA	2708
19029	AAAGCUUAUUAUUAUUAUUA	1058	19029	AAAGCUUAUUAUUAUUAUUA	1058	19047	CCUCUUAUUAUUAUUAUUA	2709
19047	GAACUCUUAUUAUUAUUAUUA	1059	19047	GAACUCUUAUUAUUAUUAUUA	1059	19065	CAUUAAGAAUUAUUAUUAUUA	2710
19065	GUACACAUUAUUAUUAUUAUUA	1060	19065	GUACACAUUAUUAUUAUUAUUA	1060	19083	AUUUAUCGUGAUUGUUAUUA	2711
19083	UUCACUGAUUGGUUAUUAUUA	1061	19083	UUCACUGAUUGGUUAUUAUUA	1061	19101	AACAACACCAUUAUUAUUA	2712
19101	UUGUUUUGGAAUUAUUAUUA	1062	19101	UUGUUUUGGAAUUAUUAUUA	1062	19119	CGUUAUUAUUAUUAUUAUUA	2713
19119	GUUGAUCGUUAUUAUUAUUA	1063	19119	GUUGAUCGUUAUUAUUAUUA	1063	19137	UGGUGGGUUAUUAUUAUUA	2714
19137	AUUGCAUUAUUAUUAUUAUUA	1064	19137	AUUGCAUUAUUAUUAUUAUUA	1064	19155	ACUACACACAUUAUUAUUA	2715
19155	UUGACACAAUUAUUAUUAUUA	1065	19155	UUGACACAAUUAUUAUUAUUA	1065	19173	ACAAACACUUAUUAUUAUUA	2716
19173	UCAAACUUAUUAUUAUUAUUA	1066	19173	UCAAACUUAUUAUUAUUAUUA	1066	19191	CUGGUAAGUUAUUAUUAUUA	2717
19191	GGCUGAUGGUUAUUAUUAUUA	1067	19191	GGCUGAUGGUUAUUAUUAUUA	1067	19209	AACUACCAUUAUUAUUAUUA	2718
19209	UUGUAUGGAAUUAUUAUUAUUA	1068	19209	UUGUAUGGAAUUAUUAUUAUUA	1068	19227	CAUGCUUAUUAUUAUUAUUA	2719
19227	GCAUUAUUAUUAUUAUUAUUA	1069	19227	GCAUUAUUAUUAUUAUUAUUA	1069	19245	AAGCUGGAGUUAUUAUUAUUA	2720
19245	UUCGAUUAUUAUUAUUAUUA	1070	19245	UUCGAUUAUUAUUAUUAUUA	1070	19263	UAAUUGCAGUUAUUAUUAUUA	2721
19263	ACUAAUUAUUAUUAUUAUUA	1071	19263	ACUAAUUAUUAUUAUUAUUA	1071	19281	GCAAUUGCUUAUUAUUAUUA	2722
19281	CCUUAUUAUUAUUAUUAUUA	1072	19281	CCUUAUUAUUAUUAUUAUUA	1072	19299	CAGAAUUAUUAUUAUUAUUA	2723
19299	GAUAGUCCUUAUUAUUAUUA	1073	19299	GAUAGUCCUUAUUAUUAUUA	1073	19317	GAGACUCACAAUUAUUAUUA	2724
19317	CAUGGCAUUAUUAUUAUUAUUA	1074	19317	CAUGGCAUUAUUAUUAUUAUUA	1074	19335	ACACUUAUUAUUAUUAUUA	2725
19335	UCGGAUUAUUAUUAUUAUUA	1075	19335	UCGGAUUAUUAUUAUUAUUA	1075	19353	GAACAUUAUUAUUAUUAUUA	2726
19353	CCACUUAUUAUUAUUAUUAUUA	1076	19353	CCACUUAUUAUUAUUAUUAUUA	1076	19371	ACGUAUUAUUAUUAUUAUUA	2727
19371	UGUAUUAUUAUUAUUAUUAUUA	1077	19371	UGUAUUAUUAUUAUUAUUAUUA	1077	19389	AUUUGCAUUAUUAUUAUUA	2728
19389	UUAUGGUGGUUAUUAUUAUUA	1078	19389	UUAUGGUGGUUAUUAUUAUUA	1078	19407	UGCAAAUUAUUAUUAUUAUUA	2729
19407	AGACACCAUUAUUAUUAUUAUUA	1079	19407	AGACACCAUUAUUAUUAUUAUUA	1079	19425	ACUUAUUAUUAUUAUUAUUA	2730
19425	UACCGACAGUUAUUAUUAUUA	1080	19425	UACCGACAGUUAUUAUUAUUA	1080	19443	CAUUAUUAUUAUUAUUAUUA	2731
19443	GCAUUAUUAUUAUUAUUAUUA	1081	19443	GCAUUAUUAUUAUUAUUAUUA	1081	19461	AAUUAUUAUUAUUAUUAUUA	2732
19461	UCUGCUGGAUUAUUAUUAUUA	1082	19461	UCUGCUGGAUUAUUAUUAUUA	1082	19479	AUAGGCUUAUUAUUAUUAUUA	2733
19479	UGGAUUAUUAUUAUUAUUAUUA	1083	19479	UGGAUUAUUAUUAUUAUUAUUA	1083	19497	CAAUUAUUAUUAUUAUUAUUA	2734
19497	GAUUAUUAUUAUUAUUAUUAUUA	1084	19497	GAUUAUUAUUAUUAUUAUUAUUA	1084	19515	UCCACAGGUUAUUAUUAUUA	2735
19515	AAUUAUUAUUAUUAUUAUUAUUA	1085	19515	AAUUAUUAUUAUUAUUAUUAUUA	1085	19533	GUAAUUAUUAUUAUUAUUAUUA	2736
19533	CAGAGUUAUUAUUAUUAUUAUUA	1086	19533	CAGAGUUAUUAUUAUUAUUAUUA	1086	19551	CCACAUUAUUAUUAUUAUUAUUA	2737

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19551	GCUIAUAUUGUUAUA	1087	19551	GCUIAUAUUGUUAUA	1087	19569	UAUUAACAUAUAAGC	2738
19569	AAAGGACACUUAUGGAC	1088	19569	AAAGGACACUUAUGGAC	1088	19587	GUCAUCAAAGUCCUUU	2739
19587	CAGCGCGGGAAGCACCUG	1089	19587	CAGCGCGGGAAGCACCUG	1089	19605	CAGUGUUGCGCGGCGUG	2740
19605	GUUCCAUUAUAUAUG	1090	19605	GUUCCAUUAUAUAUG	1090	19623	CAUUAUAUAUAUAAG	2741
19623	GCUGUUAACAAAGGUAG	1091	19623	GCUGUUAACAAAGGUAG	1091	19641	CUACCUUUGUGUAAACAGC	2742
19641	GAUGGUUAUGUGGAGA	1092	19641	GAUGGUUAUGUGGAGA	1092	19659	UCUCACAUUAUACCAUC	2743
19659	AUCUUUGAAUAAGACAA	1093	19659	AUCUUUGAAUAAGACAA	1093	19677	UUGUCUAUUUUUCAAAGAU	2744
19677	ACAUUUGCUUAUAUGUG	1094	19677	ACAUUUGCUUAUAUGUG	1094	19695	CAACAUUAACAGAAAGUGU	2745
19695	GCAUUGAGCUUUGGCGUA	1095	19695	GCAUUGAGCUUUGGCGUA	1095	19713	UAGCCAAAGCUCAAUUGC	2746
19713	AAGCGUAACAUUAAGCAG	1096	19713	AAGCGUAACAUUAAGCAG	1096	19731	CUGGUUAUAUGUACGCUU	2747
19731	GUGCCAGAUUAAGAUAC	1097	19731	GUGCCAGAUUAAGAUAC	1097	19749	GUACUUAUUCUCUGGCAC	2748
19749	CUCAUAUAUUGGUGUUG	1098	19749	CUCAUAUAUUGGUGUUG	1098	19767	CAACACCCAAUAUAUUGAG	2749
19767	GAUUCGCGCUUAUAUCUG	1099	19767	GAUUCGCGCUUAUAUCUG	1099	19785	CAGUAUUAAGCAGCGAUAC	2750
19785	GUUAUCUGGACUACAAA	1100	19785	GUUAUCUGGACUACAAA	1100	19803	UUUUGUAGUCCAGAUUAC	2751
19803	AGAGAAGCCCGACCAUG	1101	19803	AGAGAAGCCCGACCAUG	1101	19821	CAUGUGCGGGCUUCUCU	2752
19821	GUUAUCUUAAGGUGUCU	1102	19821	GUUAUCUUAAGGUGUCU	1102	19839	AGACCCUAUUGUAUAUAC	2753
19839	UGCAUAUAGUCACAUUG	1103	19839	UGCAUAUAGUCACAUUG	1103	19857	CAUUGCAGUUAUUGUACA	2754
19857	GCCAAGAACCCUACUGAGA	1104	19857	GCCAAGAACCCUACUGAGA	1104	19875	UCUCAGUAGGUUUCUUGGC	2755
19875	AGUGCUUUGUUCUACUUA	1105	19875	AGUGCUUUGUUCUACUUA	1105	19893	UAGUGAAGAACAAGACACU	2756
19893	ACUGUCUUGUUAUGGUA	1106	19893	ACUGUCUUGUUAUGGUA	1106	19911	UACCAUUAACAAGACAGU	2757
19911	AGAGUGGAAGGACAGUAG	1107	19911	AGAGUGGAAGGACAGUAG	1107	19929	CUACCGUCCUCCACUCU	2758
19929	GACCUUUUAAGAACGCC	1108	19929	GACCUUUUAAGAACGCC	1108	19947	GGCGUUCUUAAGAACGUC	2759
19947	CGUAUUGGUGUUAUAUA	1109	19947	CGUAUUGGUGUUAUAUA	1109	19965	UUAUUAACAACCAUUAACG	2760
19965	ACAGAAGGUUCAGUCAAG	1110	19965	ACAGAAGGUUCAGUCAAG	1110	19983	CUUUGACUGAACCUUCUGU	2761
19983	GGUCUACACCUUCAAAG	1111	19983	GGUCUACACCUUCAAAG	1111	20001	CCUUUGAAGGUUAUAGAC	2762
20001	GGACCAGCAAGCUAGCG	1112	20001	GGACCAGCAAGCUAGCG	1112	20019	CGUAGCUUGUGUUGGUC	2763
20019	GUCAUUGGAGUACAUUA	1113	20019	GUCAUUGGAGUACAUUA	1113	20037	UUAUUGGACUCCAUUGAC	2764
20037	AUUGGAGAUACAUAAAA	1114	20037	AUUGGAGAUACAUAAAA	1114	20055	UUUUUACUGAUUCCCAAU	2765
20055	ACACAGUUUAACUUAUA	1115	20055	ACACAGUUUAACUUAUA	1115	20073	UAAAGUUAUAACUUGUGU	2766
20073	AAGAAAGUAGCGGCAUUA	1116	20073	AAGAAAGUAGCGGCAUUA	1116	20091	UAAUGCCGUCUACUUAUUCU	2767
20091	AUUCACAGUUGCCUGAAA	1117	20091	AUUCACAGUUGCCUGAAA	1117	20109	UUUCAGGCAACUUGUUAU	2768
20109	ACCUACUUUACUCAGAGCA	1118	20109	ACCUACUUUACUCAGAGCA	1118	20127	UGCUCUGAGUAAAGUAGGU	2769
20127	AGAGACUUAAGGUAUUA	1119	20127	AGAGACUUAAGGUAUUA	1119	20145	UAAAUCCUUAAGUCUCU	2770
20145	AAGCCAGAUCAAAUUG	1120	20145	AAGCCAGAUCAAAUUG	1120	20163	CCAUUUUGUUAUCCGCGCU	2771
20163	GAACUGACUUAUUGGAGC	1121	20163	GAACUGACUUAUUGGAGC	1121	20181	GCUCGAGAAAGUAGUUAUC	2772
20181	CUCGCUAUGGAUUAUA	1122	20181	CUCGCUAUGGAUUAUA	1122	20199	UGAAUUAUCCAUAGCGAG	2773
20199	AUACAGCGAUUAAGCUCG	1123	20199	AUACAGCGAUUAAGCUCG	1123	20217	CGAGCUUAUAUCCGUGUAU	2774
20217	GAGGCUAUGCCUUGAAC	1124	20217	GAGGCUAUGCCUUGAAC	1124	20235	GUUCGAAAGCAUAGCCUC	2775
20235	CACACUUAUUGGAGAUU	1125	20235	CACACUUAUUGGAGAUU	1125	20253	AAUCCCAUAAACGAUGUG	2776
20253	UUCAGUCAUGGACACUUG	1126	20253	UUCAGUCAUGGACACUUG	1126	20271	CAAGUUGUCCAUAGCGAA	2777
20271	GGCGGCUUAUUAUAUGA	1127	20271	GGCGGCUUAUUAUAUGA	1127	20289	UCAUUAUAUAGAACCGCC	2778
20289	AUAGGCUUAGCCAGCGCU	1128	20289	AUAGGCUUAGCCAGCGCU	1128	20307	AGCGCUUGGCUAAGCGCUAU	2779

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20307	UCACAAGAUUCCACCUUA	1129	20307	UCACAAGAUUCCACCUUA	1129	20325	UAAUGUGGUAUUCUUGUA	2780
20325	AAAUAGAGUUAUUAUCC	1130	20325	AAAUAGAGUUAUUAUCC	1130	20343	GGAUAAAUCUCUAAUUG	2781
20343	CCUAGGACAGCAGUGA	1131	20343	CCUAGGACAGCAGUGA	1131	20361	UCAGUGUGUGUCCUAGG	2782
20361	AAAAUUAUUAUAACAG	1132	20361	AAAAUUAUUAUAACAG	1132	20379	CUGUUAUGAAGUAUUUUU	2783
20379	GAUGGCAACAGGUUAU	1133	20379	GAUGGCAACAGGUUAU	1133	20397	AUGAACCUUGUUGGCAUC	2784
20397	UCAAUUGUGUGUUCUG	1134	20397	UCAAUUGUGUGUUCUG	1134	20415	CAGAACACACAUUUUGA	2785
20415	GUGAUUGAUUUUAUUG	1135	20415	GUGAUUGAUUUUAUUG	1135	20433	CAAGUAAAACAUUUAU	2786
20433	GAUGAUUUGUGGAGUAA	1136	20433	GAUGAUUUGUGGAGUAA	1136	20451	UUAUCUGCAAAAGUCAUC	2787
20451	AUAAAGUCACAAGAUUGU	1137	20451	AUAAAGUCACAAGAUUGU	1137	20469	ACAAUUCUGAGACUUUAU	2788
20469	UCAGUGAUUCAAAGUGG	1138	20469	UCAGUGAUUCAAAGUGG	1138	20487	CCACUUUUGAAUACACUGA	2789
20487	GUCAGGUUAUUAUUGACU	1139	20487	GUCAGGUUAUUAUUGACU	1139	20505	AGUCAAUUGUAACCUUGAC	2790
20505	UAUGUGAAUUAUUAUUA	1140	20505	UAUGUGAAUUAUUAUUA	1140	20523	UGAAUGAAUUAUUAUUA	2791
20523	AUGCUUUGGUAAGGAUG	1141	20523	AUGCUUUGGUAAGGAUG	1141	20541	CAUCCUUAACCAAAAGCAU	2792
20541	GGACAUGUUGAAACCUUCU	1142	20541	GGACAUGUUGAAACCUUCU	1142	20559	AGAAGGUUUAACAUUGUCC	2793
20559	UACCCAAACUAACAGCAA	1143	20559	UACCCAAACUAACAGCAA	1143	20577	UUGCUUUGAUGUUUUGGUA	2794
20577	AGUCGAGUGGCAACCAAG	1144	20577	AGUCGAGUGGCAACCAAG	1144	20595	CUGUUGCCACGUCGACU	2795
20595	GGUGUUGCGAUGCUAAU	1145	20595	GGUGUUGCGAUGCUAAU	1145	20613	AGUAGGCAUCGCAACACC	2796
20613	UUGUACAAGAUUGCAAGAA	1146	20613	UUGUACAAGAUUGCAAGAA	1146	20631	UUCUUUGCAUCUUGUACAA	2797
20631	AUGCUUUGUAAAAGUGUG	1147	20631	AUGCUUUGUAAAAGUGUG	1147	20649	CACACUUUUAAGAAAGCAU	2798
20649	GACCUACAGUUAUUGGUG	1148	20649	GACCUACAGUUAUUGGUG	1148	20667	CACCAUUAUUGUAGGUC	2799
20667	GAAUUGCUGUUAUACCAA	1149	20667	GAAUUGCUGUUAUACCAA	1149	20685	UUGGUUAACAGCAUUAUUC	2800
20685	AAAGGAUUAUGAUGAUG	1150	20685	AAAGGAUUAUGAUGAUG	1150	20703	CAUUAUCAUUAUUCUUU	2801
20703	GUCGCAAGUAUACUACAC	1151	20703	GUCGCAAGUAUACUACAC	1151	20721	GUUGAGUAUACUUAUGGAC	2802
20721	CUGUGCAUUAUUAUUA	1152	20721	CUGUGCAUUAUUAUUA	1152	20739	UAUUUAAGUAUUAACACAG	2803
20739	ACACUUAUUAUGUGUAC	1153	20739	ACACUUAUUAUGUGUAC	1153	20757	GUACAGCUAAAGUAAGUGU	2804
20757	CCUACAACAUAGAGUUA	1154	20757	CCUACAACAUAGAGUUA	1154	20775	UAACUCUCAUUGUUGAGGG	2805
20775	AUUCACUUGGUGUGGCU	1155	20775	AUUCACUUGGUGUGGCU	1155	20793	AGCCAGCACCAAGUAGAU	2806
20793	UCUGAUAAAGGAGUUGCAC	1156	20793	UCUGAUAAAGGAGUUGCAC	1156	20811	GUGCAACUCUUAUACAG	2807
20811	CCAGGUACAGCUGUGCUA	1157	20811	CCAGGUACAGCUGUGCUA	1157	20829	UGAGCACAGCUGUACCGUG	2808
20829	AGACAAUGGUUGCCAAUCG	1158	20829	AGACAAUGGUUGCCAAUCG	1158	20847	CAGUUGGCAACCAUUGUCU	2809
20847	GGCACACUACUUGUGCAU	1159	20847	GGCACACUACUUGUGCAU	1159	20865	AUUCGACAAGUAGUGGCC	2810
20865	UCAGAUUUAUAGACUUGC	1160	20865	UCAGAUUUAUAGACUUGC	1160	20883	CGAAGUCAUUAAGAUUGA	2811
20883	GUCUCCGACGCAUUAUCUA	1161	20883	GUCUCCGACGCAUUAUCUA	1161	20901	UAGAUUAUGGUGGAGAG	2812
20901	ACUUAUUAUGGAGACUGU	1162	20901	ACUUAUUAUGGAGACUGU	1162	20919	CACAGUCUCCAAUUAAGU	2813
20919	GCAACAGUACAUCGGCUA	1163	20919	GCAACAGUACAUCGGCUA	1163	20937	UAGCCGUAGUACUUGUUGC	2814
20937	AUUAUUGGAGCCUUAUUA	1164	20937	AUUAUUGGAGCCUUAUUA	1164	20955	UAUAAGGUGCCAUUUUAU	2815
20955	AUUAAGGAUUAUGUAGCC	1165	20955	AUUAAGGAUUAUGUAGCC	1165	20973	GGUCAUACAUAUGCUAAU	2816
20973	CCUAGGACCAACAUUGA	1166	20973	CCUAGGACCAACAUUGA	1166	20991	UCACAUUUUUGGUCUAGG	2817
20991	ACAAGAGAAUAGACUUA	1167	20991	ACAAGAGAAUAGACUUA	1167	21009	UCAGUUAUUGCUUUUUU	2818
21009	AAAGAAAGGUUUUUCACU	1168	21009	AAAGAAAGGUUUUUCACU	1168	21027	AAGUGAAAACCCUUCUUU	2819
21027	UAUCUGUGGUAUUAUUA	1169	21027	UAUCUGUGGUAUUAUUA	1169	21045	UUUAUUAUCCACACAGUA	2820
21045	AAGCAAAACUAGCCUUG	1170	21045	AAGCAAAACUAGCCUUG	1170	21063	CCAGGGCUAGUUUUUUGCUU	2821

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21063	GGUGGUUCUAAGCUGUAA	1171	21063	GGUGGUUCUAAGCUGUAA	1171	21081	UUAAGCUUAUAGAACCC	2822
21081	AAGAUACAGACCAUUCU	1172	21081	AAGAUACAGACCAUUCU	1172	21089	AAGAUAGCUCUGUAUUCU	2823
21099	UGGAUAGCAGACCAUUCU	1173	21099	UGGAUAGCAGACCAUUCU	1173	21117	UGAUAAGGCGCAUUAUCC	2824
21117	AGCUUAUAGGCGCAUUCU	1174	21117	AGCUUAUAGGCGCAUUCU	1174	21135	AGAAUAGGCGCAUUAUCC	2825
21135	UCAUGGUGGACAGCUUUG	1175	21135	UCAUGGUGGACAGCUUUG	1175	21153	CAAAAGCUGUCCACCAUGA	2826
21153	GUUACAAUUAUUAUUAU	1176	21153	GUUACAAUUAUUAUUAU	1176	21171	AUGCAUUAUUAUUAUUAU	2827
21171	UCAUUAUUAUUAUUAU	1177	21171	UCAUUAUUAUUAUUAU	1177	21189	AAAAGUUAUUAUUAUUAU	2828
21189	UUAUUAUUAUUAUUAU	1178	21189	UUAUUAUUAUUAUUAU	1178	21207	GAUUAUUAUUAUUAUUAU	2829
21207	CUUGGACCGGACCAUUA	1179	21207	CUUGGACCGGACCAUUA	1179	21225	GUUCCUUAUUAUUAUUAU	2830
21225	CAAAUUAUUAUUAUUAU	1180	21225	CAAAUUAUUAUUAUUAU	1180	21243	UGGUAUUAUUAUUAUUAU	2831
21243	AUGCAUUAUUAUUAUUAU	1181	21243	AUGCAUUAUUAUUAUUAU	1181	21261	AAUUAUUAUUAUUAUUAU	2832
21261	UUCUGGAGGACCAUUAU	1182	21261	UUCUGGAGGACCAUUAU	1182	21279	GAUUAUUAUUAUUAUUAU	2833
21279	CUUUAUUAUUAUUAUUAU	1183	21279	CUUUAUUAUUAUUAUUAU	1183	21297	AGGAUUAUUAUUAUUAU	2834
21297	UUAUUAUUAUUAUUAU	1184	21297	UUAUUAUUAUUAUUAU	1184	21315	UCAUUAUUAUUAUUAU	2835
21315	AGCAUUAUUAUUAUUAU	1185	21315	AGCAUUAUUAUUAUUAU	1185	21333	AUUAUUAUUAUUAUUAU	2836
21333	UUAUUAUUAUUAUUAU	1186	21333	UUAUUAUUAUUAUUAU	1186	21351	UUAUUAUUAUUAUUAU	2837
21351	AUGUUAUUAUUAUUAU	1187	21351	AUGUUAUUAUUAUUAU	1187	21369	GAUUAUUAUUAUUAUUAU	2838
21369	CAAAUUAUUAUUAUUAU	1188	21369	CAAAUUAUUAUUAUUAU	1188	21387	AAUUAUUAUUAUUAUUAU	2839
21387	UUAUUAUUAUUAUUAU	1189	21387	UUAUUAUUAUUAUUAU	1189	21405	CUUUAUUAUUAUUAUUAU	2840
21405	GGUUAUUAUUAUUAUUAU	1190	21405	GGUUAUUAUUAUUAUUAU	1190	21423	CUCUUAUUAUUAUUAUUAU	2841
21423	GAUUAUUAUUAUUAUUAU	1191	21423	GAUUAUUAUUAUUAUUAU	1191	21441	CAAAUUAUUAUUAUUAUUAU	2842
21441	GUUUAUUAUUAUUAUUAU	1192	21441	GUUUAUUAUUAUUAUUAU	1192	21459	CAAAUUAUUAUUAUUAUUAU	2843
21459	GUUUAUUAUUAUUAUUAU	1193	21459	GUUUAUUAUUAUUAUUAU	1193	21477	UGUUAUUAUUAUUAUUAU	2844
21477	AUGUUAUUAUUAUUAUUAU	1194	21477	AUGUUAUUAUUAUUAUUAU	1194	21495	AUAUUAUUAUUAUUAUUAU	2845
21495	UUAUUAUUAUUAUUAUUAU	1195	21495	UUAUUAUUAUUAUUAUUAU	1195	21513	CACUUAUUAUUAUUAUUAU	2846
21513	GGUUAUUAUUAUUAUUAU	1196	21513	GGUUAUUAUUAUUAUUAU	1196	21531	ACCGUUAUUAUUAUUAUUAU	2847
21531	UGCAUUAUUAUUAUUAUUAU	1197	21531	UGCAUUAUUAUUAUUAUUAU	1197	21549	CAUUAUUAUUAUUAUUAUUAU	2848
21549	GUUUAUUAUUAUUAUUAU	1198	21549	GUUUAUUAUUAUUAUUAU	1198	21567	UGUUAUUAUUAUUAUUAUUAU	2849
21567	ACUUAUUAUUAUUAUUAU	1199	21567	ACUUAUUAUUAUUAUUAU	1199	21585	UAGUUAUUAUUAUUAUUAUUAU	2850
21585	AUGUUAUUAUUAUUAUUAU	1200	21585	AUGUUAUUAUUAUUAUUAU	1200	21603	GAUUAUUAUUAUUAUUAUUAU	2851
21603	CCUUAUUAUUAUUAUUAUUAU	1201	21603	CCUUAUUAUUAUUAUUAUUAU	1201	21621	AUCUUAUUAUUAUUAUUAUUAU	2852
21621	UCAGUUAUUAUUAUUAUUAU	1202	21621	UCAGUUAUUAUUAUUAUUAU	1202	21639	UUAUUAUUAUUAUUAUUAUUAU	2853
21639	ACUUAUUAUUAUUAUUAUUAU	1203	21639	ACUUAUUAUUAUUAUUAUUAU	1203	21657	GAUUAUUAUUAUUAUUAUUAUUAU	2854
21657	CAUUAUUAUUAUUAUUAUUAU	1204	21657	CAUUAUUAUUAUUAUUAUUAU	1204	21675	UUAUUAUUAUUAUUAUUAUUAUUAU	2855
21675	ACAGUUAUUAUUAUUAUUAUUAU	1205	21675	ACAGUUAUUAUUAUUAUUAUUAU	1205	21693	UUAUUAUUAUUAUUAUUAUUAUUAU	2856
21693	AAUUAUUAUUAUUAUUAUUAUUAU	1206	21693	AAUUAUUAUUAUUAUUAUUAUUAU	1206	21711	GGUUAUUAUUAUUAUUAUUAUUAUUAU	2857
21711	CCUUAUUAUUAUUAUUAUUAUUAU	1207	21711	CCUUAUUAUUAUUAUUAUUAUUAU	1207	21729	CCUUAUUAUUAUUAUUAUUAUUAUUAU	2858
21729	GAUUAUUAUUAUUAUUAUUAUUAU	1208	21729	GAUUAUUAUUAUUAUUAUUAUUAU	1208	21747	CAGUUAUUAUUAUUAUUAUUAUUAUUAU	2859
21747	GCAUUAUUAUUAUUAUUAUUAUUAU	1209	21747	GCAUUAUUAUUAUUAUUAUUAUUAU	1209	21765	CAUUAUUAUUAUUAUUAUUAUUAUUAU	2860
21765	GUUUAUUAUUAUUAUUAUUAUUAUUAU	1210	21765	GUUUAUUAUUAUUAUUAUUAUUAUUAU	1210	21783	AAUUAUUAUUAUUAUUAUUAUUAUUAU	2861
21783	UUUUAUUAUUAUUAUUAUUAUUAUUAU	1211	21783	UUUUAUUAUUAUUAUUAUUAUUAUUAU	1211	21801	UGUUAUUAUUAUUAUUAUUAUUAUUAU	2862
21801	AUAUUAUUAUUAUUAUUAUUAUUAUUAU	1212	21801	AUAUUAUUAUUAUUAUUAUUAUUAUUAU	1212	21819	UCACUUAUUAUUAUUAUUAUUAUUAUUAU	2863

21819	AUUAUUUUAAACAAUUCUA	1213	21819	AUUUUUUAAACAAUUCUA	1213	21837	UAGAAUUUGUUAAUAAUAAU	2864
21837	ACUAAUGUUGUUUAJACGAG	1214	21837	ACUAAUGUUGUUUAJACGAG	1214	21855	CUCGUAAUAAACAACAUUJAGU	2865
21855	GGAUGUAACUUUGAAUUGU	1215	21855	GGAUGUAACUUUGAAUUGU	1215	21873	ACAAUUGCAAAGUUUACAUGC	2866
21873	CGUAGACAACCUUUCUUG	1216	21873	UGUGACAACCUUUCUUG	1216	21891	CAAAGAAAGGGUUGUCACAC	2867
21891	CGUGUUUCUAAACCCUAGG	1217	21891	CGUGUUUCUAAACCCUAGG	1217	21909	CAUGGGUUUAGAAACACGC	2868
21909	GGUACACAGACACAUACUA	1218	21909	GGUACACAGACACAUACUA	1218	21927	UAGUAIUGUCUGUUGUACC	2869
21927	AUGAAUUCGAAUUAUGCAU	1219	21927	AUGAAUUCGAAUUAUGCAU	1219	21945	ACUCAAUUUCGAAUUAUCAU	2870
21945	UUAAUUGCACUUCUGGAGU	1220	21945	UUAAUUGCACUUCUGGAGU	1220	21963	AGCGAAAUUGCAAAUAAUA	2871
21963	UACAAUUGCAUGCCUUUU	1221	21963	UACAAUUGCAUGCCUUUU	1221	21981	AAAAGGCAUCAGAAUAUGUA	2872
21981	UCGCUUGAGUUUUCACGAAA	1222	21981	UCGCUUGAGUUUUCACGAAA	1222	21999	UUUCUGAAACAUCAACGCGA	2873
21999	AAGCAGGAAUUUUUAAAC	1223	21999	AAGCAGGAAUUUUUAAAC	1223	22017	GUUUAAAAUUCUGUACUUG	2874
22017	CACUUCACGAGUUUUGUGU	1224	22017	CACUUCACGAGUUUUGUGU	1224	22035	ACACAACUCUCUGUAAGUUG	2875
22035	UUUAAAAUUAAAGAGUGGU	1225	22035	UUUAAAAUUAAAGAGUGGU	1225	22053	ACCCAUCUUUUUUUUUAAUA	2876
22053	UUUCUCUAGUUUUUAAGG	1226	22053	UUUCUCUAGUUUUUAAGG	1226	22071	CCUUUAACCAUAGAGAAAUA	2877
22071	GGCUAAUACCCUUAUAGAUG	1227	22071	GGCUAAUACCCUUAUAGAUG	1227	22089	CAUCUAUAGGUUGAUAGGCC	2878
22089	GUAGUUGGUAUCUACCUU	1228	22089	GUAGUUGGUAUCUACCUU	1228	22107	AGGUAGUAUCAGGAACUAC	2879
22107	UCUGUUUUUAACACUUGA	1229	22107	UCUGUUUUUAACACUUGA	1229	22125	UCAAAGUGUUAAACCCAGA	2880
22125	AAACCUAUUUUUAAGUUGC	1230	22125	AAACCUAUUUUUAAGUUGC	1230	22143	GCAACUUAAAAUAAGGUUU	2881
22143	CCUCUUGGUUUUAACAUAU	1231	22143	CCUCUUGGUUUUAACAUAU	1231	22161	UAUUGUUAAUUAACCAAGG	2882
22161	ACAAAUUUUAAGGCCAUUC	1232	22161	ACAAAUUUUAAGGCCAUUC	1232	22179	GAAUGGCUCUAAAAUUUGU	2883
22179	CUUACAGCCUUUUCACUCUG	1233	22179	CUUACAGCCUUUUCACUCUG	1233	22197	CAGGUGAAAAGCGCUGUAG	2884
22197	GCUCAAGACAUUUGGGGCA	1234	22197	GCUCAAGACAUUUGGGGCA	1234	22215	UGCCCCAAUUGUCUUGAGC	2885
22215	ACGUCAGCUGCAGCCUUAU	1235	22215	ACGUCAGCUGCAGCCUUAU	1235	22233	AAUAGGCUGCAGCUGACGCU	2886
22233	UUUGUUGGCUAUUUUAAAGC	1236	22233	UUUGUUGGCUAUUUUAAAGC	1236	22251	GCUUUAAUAAGCCCAACAA	2887
22251	CCAACUACAUUUUAUGCUCA	1237	22251	CCAACUACAUUUUAUGCUCA	1237	22269	UGUACUAAAAGUAGUUGG	2888
22269	AAGUAUGAUGAAAAUGGUA	1238	22269	AAGUAUGAUGAAAAUGGUA	1238	22287	UACCAUUUUAUCAUAUCUU	2889
22287	ACAACUACAGAGUCUGUUG	1239	22287	ACAACUACAGAGUCUGUUG	1239	22305	CAACGACAUUCUGAGUUGU	2890
22305	GAUUGUUCUCAAUUAUCCAC	1240	22305	GAUUGUUCUCAAUUAUCCAC	1240	22323	GUGGAUUUUGAGAACAAUC	2891
22323	CUUGCUGAACUCAAUUGCU	1241	22323	CUUGCUGAACUCAAUUGCU	1241	22341	AGCAUUIUGAUUCACGCAAG	2892
22341	UCUGUUAAGGCUUUUGAGA	1242	22341	UCUGUUAAGGCUUUUGAGA	1242	22359	UCUCAAAGCUCUUAACAGA	2893
22359	AUIGACAAAGGAUUUUAUCC	1243	22359	AUIGACAAAGGAUUUUAUCC	1243	22377	GGUAAAUUCUUUUGUCAU	2894
22377	CAGACCUCUAAUUAUAGGG	1244	22377	CAGACCUCUAAUUAUAGGG	1244	22395	CCUGAAAUAJAGGAGGUCUG	2895
22395	GUUGUUCUCCUACGGAGAU	1245	22395	GUUGUUCUCCUACGGAGAU	1245	22413	CAUUCUCUGAGGAGCAAC	2896
22413	GUUGUGAGAUUCCCUAAUA	1246	22413	GUUGUGAGAUUCCCUAAUA	1246	22431	UAUJAGGGAUCUCACAAC	2897
22431	AUUAACAACUUGUGUCCUU	1247	22431	AUUAACAACUUGUGUCCUU	1247	22449	AAGGCACAAGUUUUGUAU	2898
22449	UUUGGAGAGUUUUUUAUUG	1248	22449	UUUGGAGAGUUUUUUAUUG	1248	22467	CAUJAAAAACCCUCCCAA	2899
22467	GUJACUAAAUUCCCUUCUG	1249	22467	GUJACUAAAUUCCCUUCUG	1249	22485	CAGAAGGGAAUUUJAGUAGC	2900
22485	GUCUAUGCAUGGGAGAGAA	1250	22485	GUCUAUGCAUGGGAGAGAA	1250	22503	UUCUCUCCCAUGCAUAGAC	2901
22503	AAAAAAUUCUAAUUGUG	1251	22503	AAAAAAUUCUAAUUGUG	1251	22521	CACAAUJAGAAAUUUUUU	2902
22521	GUUGUGAUUAUCUCUGGC	1252	22521	GUUGUGAUUAUCUCUGGC	1252	22539	GCACAGUAUGAUUGUAGAG	2903
22539	CUCUACAACUACAUAUUU	1253	22539	CUCUACAACUACAUAUUU	1253	22557	AAAAUUGAGUUUGUAGAG	2904
22557	UUUACAACCUUUUAAGUCU	1254	22557	UUUACAACCUUUUAAGUCU	1254	22575	AGCACUUAAAGGUUGAAAA	2905

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22575	UAUGGCGUUCUGCCACUA	1255	22575	UAUGGCGUUCUGCCACUA	1255	22593	UAGUGGCAGAAACGCCAUA	2905
22593	AAGUUGAAUGAUUUUGCU	1256	22593	AAGUUGAAUGAUUUUGCU	1256	22611	AGCAAGAUCAUUAACUUA	2907
22611	UUCUCCAAUGUUAUGCAG	1257	22611	UUCUCCAAUGUUAUGCAG	1257	22629	CUGCAUAGCAUUGGAGAA	2908
22629	GAUUCUUUUUGUAGUAGG	1258	22629	GAUUCUUUUUGUAGUAGG	1258	22647	CCUUGACUACAAAAGAAUC	2909
22647	GGAGAUGAUGAAGACAAA	1259	22647	GGAGAUGAUGAAGACAAA	1259	22665	UUUGUCUUAUCAUUCUCC	2910
22665	AGUGCCGAGGACAAACUG	1260	22665	AGUGCCGAGGACAAACUG	1260	22683	CAGUUUGCCUGGCGCUAU	2911
22683	GGUGUUAUUGCUGAUUAU	1261	22683	GGUGUUAUUGCUGAUUAU	1261	22701	UAUAUUAUUAUUAUUAU	2912
22701	AAUUAUAAUUGCCAGAU	1262	22701	AAUUAUAAUUGCCAGAU	1262	22719	CAUCUGGCAUUAUUAUUA	2913
22719	GAUUCAUGGUUGUGUCC	1263	22719	GAUUCAUGGUUGUGUCC	1263	22737	GGACAACCCCAUGAAUUC	2914
22737	CUUGCUUGGAUUAUAGGA	1264	22737	CUUGCUUGGAUUAUAGGA	1264	22755	UCCUAGUAUJCCAAAGCAAG	2915
22755	AACAUUGAUGCUACUCAA	1265	22755	AACAUUGAUGCUACUCAA	1265	22773	UUGAAGUAGCAUCAUUGUU	2916
22773	ACUGGUAUUAUUAUUAU	1266	22773	ACUGGUAUUAUUAUUAU	1266	22791	UAUAUUAUUAUUAUUAU	2917
22791	AAUUAUAGGUACUUAAGAC	1267	22791	AAUUAUAGGUACUUAAGAC	1267	22809	GUCUAAGAUACCUAUUAUU	2918
22809	CAUGGCAAGCUUAGGCCCU	1268	22809	CAUGGCAAGCUUAGGCCCU	1268	22827	AGGCCUUAAGCUUAGGCCAUG	2919
22827	UUUGAGAGAGACAUAUCUA	1269	22827	UUUGAGAGAGACAUAUCUA	1269	22845	UAGAUUGUCUCUCUCUCAA	2920
22845	AAUGGCCUUCUCCGCCUG	1270	22845	AAUGGCCUUCUCCGCCUG	1270	22863	CAGGGGAGAAAGGCCAAU	2921
22863	GAUGGCAACCCUUGCACCC	1271	22863	GAUGGCAACCCUUGCACCC	1271	22881	GGGUGCAAGGUUUGGCCAUC	2922
22881	CCACCUGCUCUUAUUGUU	1272	22881	CCACCUGCUCUUAUUGUU	1272	22899	AACAUAUUAAGAGCAGGUGG	2923
22899	UAUUGGCCAUUAUUAUUAU	1273	22899	UAUUGGCCAUUAUUAUUAU	1273	22917	AAUCAUUAUUAUUGGCCAAU	2924
22917	UAUGGUUUUAACACACUA	1274	22917	UAUGGUUUUAACACACUA	1274	22935	UAGUGGUUAUUAUUAUUAU	2925
22935	ACUGGCAUUGGCUAGCAAC	1275	22935	ACUGGCAUUGGCUAGCAAC	1275	22953	GUUGUAGCCAAUUGGCCAGU	2926
22953	CCUACAGAGUUGUAGUAC	1276	22953	CCUACAGAGUUGUAGUAC	1276	22971	GUACUACACUCUGUUAAGG	2927
22971	CUUUCUUUUGAACUUUUA	1277	22971	CUUUCUUUUGAACUUUUA	1277	22989	UUAAGAUAUUAUUAUUAU	2928
22989	AAUGCACCGCCACCGUUU	1278	22989	AAUGCACCGCCACCGUUU	1278	23007	AAACCGUGGCGGUGGCUAU	2929
23007	UGUGGACCAAAUUAUCCA	1279	23007	UGUGGACCAAAUUAUCCA	1279	23025	UGGAUUAUUAUUGGUCCACA	2930
23025	ACUGACCUUAUUAAGAAC	1280	23025	ACUGACCUUAUUAAGAAC	1280	23043	GGUUCUUAUUAUUAUUAU	2931
23043	CAGUGUGCAUUAUUAUUA	1281	23043	CAGUGUGCAUUAUUAUUA	1281	23061	AAUUAUUAUUAUUAUUAU	2932
23061	UUUAUUGGACUACUGGUA	1282	23061	UUUAUUGGACUACUGGUA	1282	23079	UACCAGUGAGUCCAUUAAA	2933
23079	ACUGGUGUUAUUAUUAU	1283	23079	ACUGGUGUUAUUAUUAU	1283	23097	AAGGAGUUAACACACACAGU	2934
23097	UCUUCAAAGAGAUUUAAC	1284	23097	UCUUCAAAGAGAUUUAAC	1284	23115	GUUGAAUUCUUAUUAUUA	2935
23115	CCAUUUCACAAUUAUUGCC	1285	23115	CCAUUUCACAAUUAUUGCC	1285	23133	GGCCAAUUAUUAUUAUUAU	2936
23133	CGUGAUGUUAUUAUUAUUA	1286	23133	CGUGAUGUUAUUAUUAUUA	1286	23151	UGAAUUCAGAAACAUACAG	2937
23151	ACUGAUUCCGUUUGGAGAU	1287	23151	ACUGAUUCCGUUUGGAGAU	1287	23169	GAUCUCGAACCGGAUACAGU	2938
23169	CCUAAACAUUCUGAAUUAU	1288	23169	CCUAAACAUUCUGAAUUAU	1288	23187	AUAUUAUUAUUAUUAUUAU	2939
23187	UAAGACAUUUCACCUUUGCG	1289	23187	UAAGACAUUUCACCUUUGCG	1289	23205	CGCAAGGUGAAUUAUUAU	2940
23205	GCUUUUGGGUGUUAUUAU	1290	23205	GCUUUUGGGUGUUAUUAU	1290	23223	CACUUAACCCCAAAAGC	2941
23223	GUAAUUAACCCUGGAACAA	1291	23223	GUAAUUAACCCUGGAACAA	1291	23241	UUGUCCAGGUGUUAUUAU	2942
23241	AAUGCUUAUUAUUAUUAU	1292	23241	AAUGCUUAUUAUUAUUAU	1292	23259	CAACUUCAGAUUAUUAUUA	2943
23259	CGUGUUCUUAUUAUUAUUA	1293	23259	CGUGUUCUUAUUAUUAUUA	1293	23277	CAUCUUGAUUAUUAUUAU	2944
23277	GUUAACUGCACUGAUUUUU	1294	23277	GUUAACUGCACUGAUUUUU	1294	23295	AAACAUCAGUCAGUUAAC	2945
23295	UCUACAGCAUUAUUAUUAU	1295	23295	UCUACAGCAUUAUUAUUAU	1295	23313	CUGCAUGAAUUAUUAUUAU	2946
23313	GAUCAACUCACACACGCUU	1296	23313	GAUCAACUCACACACGCUU	1296	23331	AAGCUGGUGUGAGUUAUUA	2947

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23331	UGGCGCAUAUAUUCUACUG	1297	23331	UGGCGCAUAUAUUCUACUG	1297	23349	CAGUAGAAUAUAUUGCGCCA	2948
23349	GGAACAAUAUAUUCUACUG	1298	23349	GGAACAAUAUAUUCUACUG	1298	23367	UCUGAAUAUAUUGUUUCC	2949
23367	ACUAAGCAGGUGUUA	1299	23367	ACUAAGCAGGUGUUA	1299	23385	UAGACAGCCUGCUUGAGU	2950
23385	AUAGGAGCAGGAGUUGC	1300	23385	AUAGGAGCAGGAGUUGC	1300	23403	CGACAGCUCAGCCUUAU	2951
23403	GACACUUAUAUAGAGUGCG	1301	23403	GACACUUAUAUAGAGUGCG	1301	23421	CGCACUCAUAAGAAGUGUC	2952
23421	GACAUUCUUAUUGAGCUG	1302	23421	GACAUUCUUAUUGAGCUG	1302	23439	CAGCUCUUAUAAGAAGUGUC	2953
23439	GGCAUUGUGCUAGUUAAC	1303	23439	GGCAUUGUGCUAGUUAAC	1303	23457	GGUAACUAGCAAAAGGCC	2954
23457	CAUACAGUUAUUAUUAAC	1304	23457	CAUACAGUUAUUAUUAAC	1304	23475	GUAAUAAAGAAACUGUAUG	2955
23475	CGUAGUACUAGCCAAAUA	1305	23475	CGUAGUACUAGCCAAAUA	1305	23493	AUUUUUGGUAGUACUACG	2956
23493	UCUAUUGUGGUUAUUAAC	1306	23493	UCUAUUGUGGUUAUUAAC	1306	23511	UAGUAAGCCCAAAUAGA	2957
23511	AUGUCUUAAGGUGCUUA	1307	23511	AUGUCUUAAGGUGCUUA	1307	23529	UAUCAGCACCUAAGAAGACU	2958
23529	AGUCAAUUGCUUAUUAAC	1308	23529	AGUCAAUUGCUUAUUAAC	1308	23547	UAGAGUAAGCAAUUGAACU	2959
23547	AUAACACCAUUGCUUAAC	1309	23547	AUAACACCAUUGCUUAAC	1309	23565	GUUAGCAUUGGUGUUAU	2960
23565	CCUACUAACUUAUUAUUA	1310	23565	CCUACUAACUUAUUAUUA	1310	23583	UAUUGAAAGUUAUUAUGG	2961
23583	AGCAUUAACUAGAAGUAA	1311	23583	AGCAUUAACUAGAAGUAA	1311	23601	UAUCUUCUGUAAGAAGCU	2962
23601	AUGCCUUAUUGCUUA	1312	23601	AUGCCUUAUUGCUUA	1312	23619	UAGCCUAUAGAAGCAGGCU	2963
23619	AAACCCUUGUAUUAUUA	1313	23619	AAACCCUUGUAUUAUUA	1313	23637	UACAUCUACGGAGGUUUU	2964
23637	AUAUGUACUUGCGGAG	1314	23637	AUAUGUACUUGCGGAG	1314	23655	CUCCGCAUUGUAUAUUA	2965
23655	GAUUCUACUGAAUGUCUA	1315	23655	GAUUCUACUGAAUGUCUA	1315	23673	UAGCACAUCAGUAGAUAUC	2966
23673	AUUUGCUUCUCCAAUAUG	1316	23673	AUUUGCUUCUCCAAUAUG	1316	23691	CAUAUUGGAGAAAGAAUCC	2967
23691	GGUAGCUUUGCACACAAC	1317	23691	GGUAGCUUUGCACACAAC	1317	23709	GUUGUGUAAAAGCUUAC	2968
23709	CUAAUUGUGCACUCUCAG	1318	23709	CUAAUUGUGCACUCUCAG	1318	23727	CUGAGAGUGCACGAUUUAG	2969
23727	GGUUAUGUGCUAGAAGG	1319	23727	GGUUAUGUGCUAGAAGG	1319	23745	CCUGUUCAGCAGCAUAUCC	2970
23745	GAUCGCAACACGUGAAG	1320	23745	GAUCGCAACACGUGAAG	1320	23763	CUUCACGUGUUGCGAUC	2971
23763	GUGUUGCUCAAGUCAAAC	1321	23763	GUGUUGCUCAAGUCAAAC	1321	23781	GUUUGACUUGAGCGGAACAC	2972
23781	CAAUUGUACAAACCCCAA	1322	23781	CAAUUGUACAAACCCCAA	1322	23799	UUGGGUUUUUGUAUAUUG	2973
23799	ACUUGAAUAUUAUUGGUG	1323	23799	ACUUGAAUAUUAUUGGUG	1323	23817	CACCAAAUAUUAUUAUUG	2974
23817	GGUUUAUUAUUAUUAUUA	1324	23817	GGUUUAUUAUUAUUAUUA	1324	23835	UUUGUGAAAAUUAUUAUCC	2975
23835	AUAUACCUAGCCUUA	1325	23835	AUAUACCUAGCCUUA	1325	23853	UUAGAGGUGCAGGUAAUAU	2976
23853	AAGCCAUAAGAGGUCUUA	1326	23853	AAGCCAUAAGAGGUCUUA	1326	23871	AAGACCUUAUAGUUGGCUU	2977
23871	UUUAUAGGACUUGCUCU	1327	23871	UUUAUAGGACUUGCUCU	1327	23889	AGAGCAAGUCCUUAUUA	2978
23889	UUUAUAGGACUUGCUCU	1328	23889	UUUAUAGGACUUGCUCU	1328	23907	CGAGUGCACCUCUUAUUA	2979
23907	GCUGAUGCGUUAUUAUUA	1329	23907	GCUGAUGCGUUAUUAUUA	1329	23925	UCAUGAGCCAGCAUUAUUA	2980
23925	AAGCAUAUUGGCAUUAUUA	1330	23925	AAGCAUAUUGGCAUUAUUA	1330	23943	GGCAUUGCCCAUUAUUAUUA	2981
23943	CUAGGUGAUUAUUAUUA	1331	23943	CUAGGUGAUUAUUAUUA	1331	23961	UAGCAUUAUUAUUAUUAUUA	2982
23961	AGAGAUUAUUAUUAUUAUUA	1332	23961	AGAGAUUAUUAUUAUUAUUA	1332	23979	GGCACAUAUUAUUAUUAUUA	2983
23979	CAGAAGUUAUUAUUAUUAUUA	1333	23979	CAGAAGUUAUUAUUAUUAUUA	1333	23997	UAAGUCCAUUAUUAUUAUUA	2984
23997	ACAGUUAUUAUUAUUAUUAUUA	1334	23997	ACAGUUAUUAUUAUUAUUAUUA	1334	24015	CGAGAGGUGGCAUUAUUAUUA	2985
24015	CUCAGUUAUUAUUAUUAUUAUUA	1335	24015	CUCAGUUAUUAUUAUUAUUAUUA	1335	24033	CAUUAUUAUUAUUAUUAUUA	2986
24033	CGUGCCUUAUUAUUAUUAUUAUUA	1336	24033	CGUGCCUUAUUAUUAUUAUUAUUA	1336	24051	GAGCAGCAGUUAUUAUUAUUA	2987
24051	CUAGUUAUUAUUAUUAUUAUUAUUA	1337	24051	CUAGUUAUUAUUAUUAUUAUUAUUA	1337	24069	UGGCAGUUAUUAUUAUUAUUAUUA	2988
24069	ACUGCUGGAUUAUUAUUAUUAUUAUUA	1338	24069	ACUGCUGGAUUAUUAUUAUUAUUAUUA	1338	24087	CAAUUGUCCAUUAUUAUUAUUAUUA	2989

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24087	GGUGCUGGCGCUCUUC	1339	24087	GGUGCUGGCGCUCUUC	1339	24105	GAAGAGCAGCGCCAGCACC	2990
24105	CAAAUACCUUUUGCUAUGC	1340	24105	CAAAUACCUUUUGCUAUGC	1340	24123	GGAUAGCAAAAGUUAUUG	2991
24123	CAAAUGGCAUAUAGGUICA	1341	24123	CAAAUGGCAUAUAGGUICA	1341	24141	UGAACCUUAUUGCCAUUUG	2992
24141	AUUGGCAUUGGAGUUAUCC	1342	24141	AUUGGCAUUGGAGUUAUCC	1342	24159	GGGUAACUCCAAUGCCAUU	2993
24159	CAAAUUGUUCUUAUGAGA	1343	24159	CAAAUUGUUCUUAUGAGA	1343	24177	UCUCAAGAGAAUUAUUG	2994
24177	AACCAAAACAAUUGCCA	1344	24177	AACCAAAACAAUUGCCA	1344	24195	UGGCGAUUUGUUUUUGGUU	2995
24195	AACCAUUAACAAGGCGA	1345	24195	AACCAUUAACAAGGCGA	1345	24213	UGGCGUUAUUAUUGGUU	2996
24213	AUUAUUAUUAUUAUUAU	1346	24213	AUUAUUAUUAUUAUUAU	1346	24231	AUUAUUAUUAUUAUUAU	2997
24231	UCACUUAACAACAUAUAA	1347	24231	UCACUUAACAACAUAUAA	1347	24249	UUAUUAUUAUUAUUAU	2998
24249	ACUGCAUUGGCAAGCUGC	1348	24249	ACUGCAUUGGCAAGCUGC	1348	24267	GCAGCUUGCCCAUUGCAGU	2999
24267	CAAGACGUUUAUUAUUAU	1349	24267	CAAGACGUUUAUUAUUAU	1349	24285	UCUGGUUAACAACGUCUUG	3000
24285	AUAGCUAAGCAUUAUUAU	1350	24285	AUAGCUAAGCAUUAUUAU	1350	24303	UGUUUAUUGCUUAGCAU	3001
24303	ACACUUGUUAACAACUUA	1351	24303	ACACUUGUUAACAACUUA	1351	24321	UAAUUAUUGUUAACAACU	3002
24321	AGCUCUUAUUAUUGGCA	1352	24321	AGCUCUUAUUAUUGGCA	1352	24339	UUGCACCACAAUUAUAGCU	3003
24339	AUUAUUAUUAUUAUUAU	1353	24339	AUUAUUAUUAUUAUUAU	1353	24357	CAUUUAUUAUUAUUAU	3004
24357	GAUUAUUAUUAUUAUUAU	1354	24357	GAUUAUUAUUAUUAUUAU	1354	24375	CAAGUCGCGAAUUAUUAU	3005
24375	GAUUAUUAUUAUUAUUAU	1355	24375	GAUUAUUAUUAUUAUUAU	1355	24393	CCUCCGCUUCCGCUUUAU	3006
24393	GUACAAUUAUUAUUAUUAU	1356	24393	GUACAAUUAUUAUUAUUAU	1356	24411	UUAACCUUGCUUUAUUAU	3007
24411	AUUAUUAUUAUUAUUAU	1357	24411	AUUAUUAUUAUUAUUAU	1357	24429	UUUAUUAUUAUUAUUAU	3008
24429	AGCCUUAUUAUUAUUAU	1358	24429	AGCCUUAUUAUUAUUAU	1358	24447	UUUAUUAUUAUUAUUAU	3009
24447	ACACAAUUAUUAUUAUUAU	1359	24447	ACACAAUUAUUAUUAUUAU	1359	24465	CCUUAUUAUUAUUAUUAU	3010
24465	GCUGCUAUAUUAUUAUUAU	1360	24465	GCUGCUAUAUUAUUAUUAU	1360	24483	AAGCCUGAUUAUUAUUAU	3011
24483	UCUGCUAUAUUAUUAUUAU	1361	24483	UCUGCUAUAUUAUUAUUAU	1361	24501	UAGCAGCAAGAUUAUUAU	3012
24501	ACUUAUUAUUAUUAUUAU	1362	24501	ACUUAUUAUUAUUAUUAU	1362	24519	CACACUCAGAUUAUUAU	3013
24519	GUUUAUUAUUAUUAUUAU	1363	24519	GUUUAUUAUUAUUAUUAU	1363	24537	UUUUUAUUAUUAUUAU	3014
24537	AGGUUAUUAUUAUUAUUAU	1364	24537	AGGUUAUUAUUAUUAUUAU	1364	24555	UUCCACAAUUAUUAUUAU	3015
24555	AAGGCUUAUUAUUAUUAU	1365	24555	AAGGCUUAUUAUUAUUAU	1365	24573	ACAAUUAUUAUUAUUAU	3016
24573	UCCUUAUUAUUAUUAUUAU	1366	24573	UCCUUAUUAUUAUUAUUAU	1366	24591	GGGCUUAUUAUUAUUAU	3017
24591	CCGUAUUAUUAUUAUUAU	1367	24591	CCGUAUUAUUAUUAUUAU	1367	24609	GGAAGCAUUAUUAUUAU	3018
24609	CUACUUAUUAUUAUUAUUAU	1368	24609	CUACUUAUUAUUAUUAUUAU	1368	24627	GCACUUAUUAUUAUUAU	3019
24627	CCAUAUUAUUAUUAUUAU	1369	24627	CCAUAUUAUUAUUAUUAU	1369	24645	AGUUAUUAUUAUUAUUAU	3020
24645	UUAUAUUAUUAUUAUUAU	1370	24645	UUAUAUUAUUAUUAUUAU	1370	24663	UUUGCUUAUUAUUAUUAU	3021
24663	AUUUAUUAUUAUUAUUAU	1371	24663	AUUUAUUAUUAUUAUUAU	1371	24681	CUUUAUUAUUAUUAUUAU	3022
24681	GCAUAUUAUUAUUAUUAU	1372	24681	GCAUAUUAUUAUUAUUAU	1372	24699	CUUUAUUAUUAUUAUUAU	3023
24699	GGUUAUUAUUAUUAUUAU	1373	24699	GGUUAUUAUUAUUAUUAU	1373	24717	CAUUAUUAUUAUUAUUAU	3024
24717	GGCAUUAUUAUUAUUAUUAU	1374	24717	GGCAUUAUUAUUAUUAUUAU	1374	24735	UUAUAUUAUUAUUAUUAU	3025
24735	ACACAGGAUUAUUAUUAU	1375	24735	ACACAGGAUUAUUAUUAU	1375	24753	AAAGAGUUAUUAUUAUUAU	3026
24753	UCUUAUUAUUAUUAUUAU	1376	24753	UCUUAUUAUUAUUAUUAU	1376	24771	UAGUAUUAUUAUUAUUAU	3027
24771	ACACAGGAUUAUUAUUAU	1377	24771	ACACAGGAUUAUUAUUAU	1377	24789	AGCAUUAUUAUUAUUAU	3028
24789	UCAGGAUUAUUAUUAUUAU	1378	24789	UCAGGAUUAUUAUUAUUAU	1378	24807	CGACUUAUUAUUAUUAU	3029
24807	GUUAUUAUUAUUAUUAUUAU	1379	24807	GUUAUUAUUAUUAUUAUUAU	1379	24825	UGUUAUUAUUAUUAUUAU	3030
24825	AACACAGUUAUUAUUAUUAU	1380	24825	AACACAGUUAUUAUUAUUAU	1380	24843	GAGGAUUAUUAUUAUUAU	3031

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24843	CUGAACCCUGAGCUUGACU	1381	24843	CUGAACCCUGAGCUUGACU	1381	24861	AGUCAAGCUCAGGUUGCAG	3032
24861	UCAUUCAAAGAGAGCUGG	1382	24861	UCAUUCAAAGAGAGCUGG	1382	24879	CGAGCUCUUCUUUGAUG	3033
24879	GACAAGUACUCAAUAUC	1383	24879	GACAAGUACUCAAUAUC	1383	24897	GAUUUUUGAAGUACUUGC	3034
24897	CAUACAUCACAGAUUG	1384	24897	CAUACAUCACAGAUUG	1384	24915	CAACAUCUGGUGAUGUAG	3035
24915	GAUCUUGGCGACAUUCAG	1385	24915	GAUCUUGGCGACAUUCAG	1385	24933	CUGAAUUGJCGCCAAAGC	3036
24933	GGCAUUAACGCUUCUGG	1386	24933	GGCAUUAACGCUUCUGG	1386	24951	CGACAAGCGGUUAAUGCC	3037
24951	GUCAACAUCAAAAGAAA	1387	24951	GUCAACAUCAAAAGAAA	1387	24969	UUUCUUUUUGAAUUGGAC	3038
24969	AUAGACCGCCUCAAUGAGG	1388	24969	AUAGACCGCCUCAAUGAGG	1388	24987	CCUAAUUGAGCGGUGCAAU	3039
24987	GUGCUAAAAUUUAAUUG	1389	24987	GUGCUAAAAUUUAAUUG	1389	25005	CAUUUAAUUUUUAGCGAC	3040
25005	GAUACACUUAUUGACCUUC	1390	25005	GAUACACUUAUUGACCUUC	1390	25023	GAAAGUCAUAGAGUUAUC	3041
25023	CAAGAAUUGGAAAUUUG	1391	25023	CAAGAAUUGGAAAUUUG	1391	25041	CAUUUUUUCCCAUUUCUUG	3042
25041	GAGCAUUAUUAUUAUUGC	1392	25041	GAGCAUUAUUAUUAUUGC	1392	25059	GCCAUUUAAUUAUUGCUC	3043
25059	CCUUGGUAUUGGCUUCG	1393	25059	CCUUGGUAUUGGCUUCG	1393	25077	CGAGCCAAACAUAACCAAGG	3044
25077	GGCUUUAUUGGCUUCG	1394	25077	GGCUUUAUUGGCUUCG	1394	25095	UUAGUCCAGCAUUAAGGCC	3045
25095	AUUGCCAUCGCUUGUUA	1395	25095	AUUGCCAUCGCUUGUUA	1395	25113	UAACCAUCAGCAUUGGCAU	3046
25113	ACAUCUUGCUUUGUUA	1396	25113	ACAUCUUGCUUUGUUA	1396	25131	UGCAACAAAGCAAGAUUGU	3047
25131	AUGACUAGUUUGCAGUU	1397	25131	AUGACUAGUUUGCAGUU	1397	25149	AACUGCAACACUAGUCAU	3048
25149	UGCCUCAAGGUGCAUGCU	1398	25149	UGCCUCAAGGUGCAUGCU	1398	25167	AGCAUGCACCUCUAGGGCA	3049
25167	UCUUGUGUUCUUGCUGCA	1399	25167	UCUUGUGUUCUUGCUGCA	1399	25185	AGCAGCAAGCAACCAAGA	3050
25185	AAGUUGAUGAGGAGACU	1400	25185	AAGUUGAUGAGGAGACU	1400	25203	AGUCAUCUUAUACCAACU	3051
25203	UCUGAGCGAUUCUACAGG	1401	25203	UCUGAGCGAUUCUACAGG	1401	25221	CCUUGAGAACUUGACAGA	3052
25221	GGUGUCAAUUAUUAUUA	1402	25221	GGUGUCAAUUAUUAUUA	1402	25239	UGUAUUGAAUUUUGACACC	3053
25239	ACAAACCAACUUAUGGA	1403	25239	ACAAACCAACUUAUGGA	1403	25257	UCCAUAAGUUCGUUUAUGU	3054
25257	UUUGUUUAUGAGUUUUU	1404	25257	UUUGUUUAUGAGUUUUU	1404	25275	AAAUAUCUAUAAACAAU	3055
25275	UUACUCUUGGAUUAUUA	1405	25275	UUACUCUUGGAUUAUUA	1405	25293	GUAAUUGAUCCAAGAGUAA	3056
25293	CUGCACAGCCAGUAAAAU	1406	25293	CUGCACAGCCAGUAAAAU	1406	25311	UUUUUACUGGUGGUGCAG	3057
25311	UUGACAUGCUUCCUGC	1407	25311	UUGACAUGCUUCCUGC	1407	25329	GCAGGAGAAGCAUUGUCAA	3058
25329	CAAGUACUGUUAUUGCUAC	1408	25329	CAAGUACUGUUAUUGCUAC	1408	25347	GUAGCAUGAACAGUACUUG	3059
25347	CAGCAACGUAUCCGCUACA	1409	25347	CAGCAACGUAUCCGCUACA	1409	25365	UGUAGCGUAUCGUUGCUG	3060
25365	AAGCCUCACUCCUUCGG	1410	25365	AAGCCUCACUCCUUCGG	1410	25383	CCGAAAGGAGUGAGGCUU	3061
25383	GAUGGCUUUAUUGGCGU	1411	25383	GAUGGCUUUAUUGGCGU	1411	25401	ACGCCAAUAAAGGCAUUC	3062
25401	UUGCAUUUCUUGCUUUAU	1412	25401	UUGCAUUUCUUGCUUUAU	1412	25419	AAACAGCAAGAAUUGCAA	3063
25419	UUCAGAGCGCUAACAAAU	1413	25419	UUCAGAGCGCUAACAAAU	1413	25437	AUUUJGGUAGCGCUGGAA	3064
25437	UAUUUGCGCUCAAUAAAG	1414	25437	UAUUUGCGCUCAAUAAAG	1414	25455	UUUUUJUGAGCGCAUUA	3065
25455	GAUGGCGCUAGCCUUUA	1415	25455	GAUGGCGCUAGCCUUUA	1415	25473	UAAAGGCGUAGCUGGCAU	3066
25473	AUAAGGCGUCCAGUUAU	1416	25473	AUAAGGCGUCCAGUUAU	1416	25491	AUGAACUGGAAGCCUUUAU	3067
25491	UUUGCAUUUACUGCUGCU	1417	25491	UUUGCAUUUACUGCUGCU	1417	25509	AGCAGCAGUAAUUGCAAA	3068
25509	UAUUUGUUAUCCAUUAUC	1418	25509	UAUUUGUUAUCCAUUAUC	1418	25527	GAUAGAUGGUAAACAAUUA	3069
25527	CACAUUUUUGCUUUGCG	1419	25527	CACAUUUUUGCUUUGCG	1419	25545	GCGAAGCAAGAAAGUUG	3070
25545	CUGCAGGUAUGGAGCGCA	1420	25545	CUGCAGGUAUGGAGCGCA	1420	25563	UGCGCCUCCAUACCGCAG	3071
25563	AUUUUUUGUACCUUAUGC	1421	25563	AUUUUUUGUACCUUAUGC	1421	25581	GCAUAGAGGUACAAAUUA	3072
25581	CCUUGAAUUAUUUUCUACA	1422	25581	CCUUGAAUUAUUUUCUACA	1422	25599	UGUAGAAAAUUAUUAUAGG	3073

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25599	AAUGCAUCAACGCAUGUAG	1423	25599	AAUGCAUCAACGCAUGUAG	1423	25617	CUACAUGCGUUGAUGCAUU	3074
25617	GAUUUAUUAUGAGAUUG	1424	25617	GAUUUAUUAUGAGAUUG	1424	25635	CAACAUCUCAUAUAUUC	3075
25635	GGUUUUGUUGAAGUGCAA	1425	25635	GGUUUUGUUGAAGUGCAA	1425	25653	UUGCACUUCACAAAGGCC	3076
25653	AAUCCAAGAACCCAUUACU	1426	25653	AAUCCAAGAACCCAUUACU	1426	25671	AGUAAUGGGUUCUUGGAUU	3077
25671	UUUAUGAUGCCCAACUACUU	1427	25671	UUUAUGAUGCCCAACUACUU	1427	25689	AAGUAGUJGGCAUCAUAAA	3078
25689	UUGUUUGCGUGCACACACA	1428	25689	UUGUUUGCGUGCACACACA	1428	25707	UGUGUGGCCAGCAACAAA	3079
25707	AUAACUAUGACUACUUAU	1429	25707	AUAACUAUGACUACUUAU	1429	25725	AUACAGUAGCAUUAUUA	3080
25725	UACCAUAUAACAGUGUCAC	1430	25725	UACCAUAUAACAGUGUCAC	1430	25743	GUGACACUGUUAUUAUGGUA	3081
25743	CAGAUACAAUUGUGUUAUAC	1431	25743	CAGAUACAAUUGUGUUAUAC	1431	25761	GUACGACAAUUGUAUCUG	3082
25761	CUGAAGGUGACGGCAUUUC	1432	25761	CUGAAGGUGACGGCAUUUC	1432	25779	GAUUAUGCGUACCUUCAG	3083
25779	CAACACCAAAACUCAAAGA	1433	25779	CAACACCAAAACUCAAAGA	1433	25797	UCUUUGAGUUUUGGUGUUG	3084
25797	AAGACUACCAAAUUGGUGG	1434	25797	AAGACUACCAAAUUGGUGG	1434	25815	CCACCAUUUUGGUAUCUU	3085
25815	GUUAUUCUGAGGAUAGGCA	1435	25815	GUUAUUCUGAGGAUAGGCA	1435	25833	UGCCUAUCCUCAGAAUAAC	3086
25833	ACUCAGGUGUUAAGACUA	1436	25833	ACUCAGGUGUUAAGACUA	1436	25851	UAGUCUUUAACACCUUGAGU	3087
25851	AUGUCUUGUACAUUGGCUA	1437	25851	AUGUCUUGUACAUUGGCUA	1437	25869	UAGCCAAUGUACACGACAU	3088
25869	AUUCACCGGAAGUUAUUA	1438	25869	AUUCACCGGAAGUUAUUA	1438	25887	UAGUAAACUUCGGUGAAU	3089
25887	ACCAGCUUGAGUCUACACA	1439	25887	ACCAGCUUGAGUCUACACA	1439	25905	UGUGUAGACUCAAGCUGGU	3090
25905	AAUUAACUACAGACACUGG	1440	25905	AAUUAACUACAGACACUGG	1440	25923	CCAGUGUCUGUAGUAAUUU	3091
25923	GUUUUGAAAAGUACAAUU	1441	25923	GUUUUGAAAAGUACAAUU	1441	25941	AAUGUAGCAUUUUCAAAUAC	3092
25941	UCUUUAACUUAACAAAGCU	1442	25941	UCUUUAACUUAACAAAGCU	1442	25959	AGCUUUGUAAAAGUAAGA	3093
25959	UUGUUUAAGACCCACCGAA	1443	25959	UUGUUUAAGACCCACCGAA	1443	25977	UUCGGUGGGUCUUUAACAA	3094
25977	AUGUGCAAAUACACACAAU	1444	25977	AUGUGCAAAUACACACAAU	1444	25995	AUUGUGUUAUUUGCAUUA	3095
25995	UCGACGGCUCUUCAGGAGU	1445	25995	UCGACGGCUCUUCAGGAGU	1445	26013	ACUCCUGAAGAGCGGUGCA	3096
26013	UUGCUAAUCCAGCAUUGGA	1446	26013	UUGCUAAUCCAGCAUUGGA	1446	26031	UCCAUUUGCGUAUUAGCAA	3097
26031	AUCCAAUUUAUGAUGGCC	1447	26031	AUCCAAUUUAUGAUGGCC	1447	26049	GGCUCAUCAUAAUUGGAU	3098
26049	CGACGACGACUACUAGCGU	1448	26049	CGACGACGACUACUAGCGU	1448	26067	ACGCUAGUAGUCGUGCGG	3099
26067	UGCCUUUGUAAGCACAAGA	1449	26067	UGCCUUUGUAAGCACAAGA	1449	26085	UCUUGUGCUUACAAAGGCA	3100
26085	AAAGUGAGUACGAACUUAU	1450	26085	AAAGUGAGUACGAACUUAU	1450	26103	AUAAGUUCGUACUCACUUU	3101
26103	UGUACUCAUUCGUUUCGGA	1451	26103	UGUACUCAUUCGUUUCGGA	1451	26121	UCCGAAACGAUUGCAUACA	3102
26121	AAGAAACAGGUACGUUAUU	1452	26121	AAGAAACAGGUACGUUAUU	1452	26139	AUUAACGUACCGUUUUCUU	3103
26139	UAGUUAUAGCGUACUUCU	1453	26139	UAGUUAUAGCGUACUUCU	1453	26157	AGAAGUACGCUAUUAACUA	3104
26157	UUUUUCUUGCUUUCGUGGU	1454	26157	UUUUUCUUGCUUUCGUGGU	1454	26175	ACCACGAAACGAAGAAAA	3105
26175	UAUUCUUGCUAGUCACACU	1455	26175	UAUUCUUGCUAGUCACACU	1455	26193	AGUGUGACUAGCAAGAAUA	3106
26193	UAGCCAUCCUUAUCUGCGCU	1456	26193	UAGCCAUCCUUAUCUGCGCU	1456	26211	AGCGCAGUAAGGAUGGCUA	3107
26211	UUCGAUUGUGUGCGUACUG	1457	26211	UUCGAUUGUGUGCGUACUG	1457	26229	CAGUACGCACACAAUCGAA	3108
26229	GCUGCAUAUUGUUAACGU	1458	26229	GCUGCAUAUUGUUAACGU	1458	26247	ACGUJAAACAAUUAUGCAGC	3109
26247	UGAGUUUAAGUAAAACCAAC	1459	26247	UGAGUUUAAGUAAAACCAAC	1459	26265	GUUGUUUUUUAUUAACUCA	3110
26265	CGGUUUACGCUACUGCGG	1460	26265	CGGUUUACGCUACUGCGG	1460	26283	CGCGAGUAGACGUAACCCG	3111
26283	GUGUUAUAAUUCUGAACUC	1461	26283	GUGUUAUAAUUCUGAACUC	1461	26301	GAGUUCAGAUUUUAACAC	3112
26301	CUUCUGAAGGAGUUCUGA	1462	26301	CUUCUGAAGGAGUUCUGA	1462	26319	UCAGGAACUCCUUGAGAAG	3113
26319	AUCUUCUGGUCUAAACGAA	1463	26319	AUCUUCUGGUCUAAACGAA	1463	26337	UUCGUUUAAGACCAAGAAU	3114
26337	ACUAACUAUUAUUAUUAU	1464	26337	ACUAACUAUUAUUAUUAU	1464	26355	AUAUAUAUUAUUAUUAU	3115

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26355	UCUGUUUGGAACUUUAACA	1465	26355	UCUGUUUGGAACUUUAACA	1465	26373	UGUAAAAGUUCCAAACAGA	3116
26373	AUUGCUUAUUAUUGGACAC	1466	26373	AUUGCUUAUUAUUGGACAC	1466	26391	GUCUCCCAUUAUAAACAAU	3117
26391	CAACGGUACUUAUACCGUU	1467	26391	CAACGGUACUUAUACCGUU	1467	26409	AACGGUUAUUAUACCGUUG	3118
26409	UGAGGAGCUUAUAAACACUC	1468	26409	UGAGGAGCUUAUAAACACUC	1468	26427	GAGUUGUUUAAGCUCCUCA	3119
26427	CCUGGAACAUAUGGAACCUA	1469	26427	CCUGGAACAUAUGGAACCUA	1469	26445	UAGGUUCCAUUUGUCCAGG	3120
26445	AGUAAGGUUUUCCUAUUC	1470	26445	AGUAAGGUUUUCCUAUUC	1470	26463	GAAUAGGAAACCUAUUACU	3121
26463	CUUAGCCUGGUAUUAUUA	1471	26463	CUUAGCCUGGUAUUAUUA	1471	26481	UAACAUAAUCCAGGCUAGG	3122
26481	ACUACAAUUUGCCUAUUCU	1472	26481	ACUACAAUUUGCCUAUUCU	1472	26499	AGAUAAGGCAAAUUGUAGU	3123
26499	UAUUCGGAACAGGUUUUUG	1473	26499	UAUUCGGAACAGGUUUUUG	1473	26517	CAAAAACCUUUGUCCGAUUA	3124
26517	GUACAAUUAUAAAGCUUGU	1474	26517	GUACAAUUAUAAAGCUUGU	1474	26535	AACAAGCUUUUAUUAUUAU	3125
26535	UUUCUUCUGGCUUUGUGG	1475	26535	UUUCUUCUGGCUUUGUGG	1475	26553	CCACAAGAGCCAGAGGAAA	3126
26553	GCCAGUAACAUUGCUUGU	1476	26553	GCCAGUAACAUUGCUUGU	1476	26571	ACAAGCAAGUGUUAUCUGGC	3127
26571	UUUUGUCUUGCUGCUGUC	1477	26571	UUUUGUCUUGCUGCUGUC	1477	26589	GACAGCAGCAAGCAACAAA	3128
26589	CUACAGAAUUAUUGGGUG	1478	26589	CUACAGAAUUAUUGGGUG	1478	26607	CACCCAAUUAUUCUGUAG	3129
26607	GACUGGCGGAUUGCGAUU	1479	26607	GACUGGCGGAUUGCGAUU	1479	26625	AAUCGCAUUCGCCGAGUC	3130
26625	UGCAAUGGCUUGUAUUGUA	1480	26625	UGCAAUGGCUUGUAUUGUA	1480	26643	UACAUAACAAGCCAUUGCA	3131
26643	AGGCUUGAUGGCUUAGC	1481	26643	AGGCUUGAUGGCUUAGC	1481	26661	GUAAAGCCACAUCAAGCCU	3132
26661	CUACUUCGUUGCUUCCUUC	1482	26661	CUACUUCGUUGCUUCCUUC	1482	26679	GAAAGGAAGCAACGAAGUAG	3133
26679	CAGGCUUAUUGGCUUAGC	1483	26679	CAGGCUUAUUGGCUUAGC	1483	26697	GGUACGAGCAAAACAGCCUG	3134
26697	CCGUCUAUUGGCUUAGC	1484	26697	CCGUCUAUUGGCUUAGC	1484	26715	GAUUGCCACAUUGAGCGG	3135
26715	CAACCCAGAAACAACAUU	1485	26715	CAACCCAGAAACAACAUU	1485	26733	AAUUGUUGUUCUGGGUUG	3136
26733	UCUUCUCAAUUGGCCUCUC	1486	26733	UCUUCUCAAUUGGCCUCUC	1486	26751	GAGAGGCACAUUGAGAAGA	3137
26751	CCGGGGACAUAUUGGAC	1487	26751	CCGGGGACAUAUUGGAC	1487	26769	GGUACAAUUGUCCCGCGG	3138
26769	CAGACCGCUAUGGAAAGU	1488	26769	CAGACCGCUAUGGAAAGU	1488	26787	ACUUCUUAUGAGCGGUCUG	3139
26787	UGAACUUGCUAUGGUGCU	1489	26787	UGAACUUGCUAUGGUGCU	1489	26805	AGCACCAUUGACAAGUUA	3140
26805	UGUAUCAUUCGUGGUCAC	1490	26805	UGUAUCAUUCGUGGUCAC	1490	26823	GUGUCCGGCCAUUCGCAAG	3141
26823	CUUUGGAUUGCCCGGACAC	1491	26823	CUUUGGAUUGCCCGGACAC	1491	26841	GUGUCCGGCCAUUCGCAAG	3142
26841	CUCCUAGGGCGCUGGAC	1492	26841	CUCCUAGGGCGCUGGAC	1492	26859	GUACAGCGCCCUAGGGAG	3143
26859	CAUUAAGGACCUGCCAAA	1493	26859	CAUUAAGGACCUGCCAAA	1493	26877	UUUUGCAGGCUCCUUAUUG	3144
26877	AGAGAUCAUUGGCUACA	1494	26877	AGAGAUCAUUGGCUACA	1494	26895	UGUAGCCACAGUGAUUCU	3145
26895	AUCACGAACGUUUCUUAU	1495	26895	AUCACGAACGUUUCUUAU	1495	26913	AUAAGAAAGGUUCGUGAU	3146
26913	UUAACAAUUAAGGACGUG	1496	26913	UUAACAAUUAAGGACGUG	1496	26931	CGACGUCCUUAUUAUUA	3147
26931	GCAGCGUUAAGGACGUGAU	1497	26931	GCAGCGUUAAGGACGUGAU	1497	26949	AUCAGUGCCUACACGCGUC	3148
26949	UUCAGGUUUUGCUGCAUAC	1498	26949	UUCAGGUUUUGCUGCAUAC	1498	26967	GUAUGCAGCAAAACCCUGAA	3149
26967	CAACCGCUACCGUAUUGGA	1499	26967	CAACCGCUACCGUAUUGGA	1499	26985	UCCAUAACGGUAGCGGUUG	3150
26985	AAACUAAUUAUUAUUA	1500	26985	AAACUAAUUAUUAUUA	1500	27003	UGUAUUUAUUAUUAUUA	3151
27003	AGACCACCGCGUAGCAAC	1501	27003	AGACCACCGCGUAGCAAC	1501	27021	GUUGCUACCGCGGUGGUCU	3152
27021	CGACAAUUAUUGCUUUA	1502	27021	CGACAAUUAUUGCUUUA	1502	27039	UAGCAAAGCAUUAUUGUG	3153
27039	AGUACAGUAAGGACAAACA	1503	27039	AGUACAGUAAGGACAAACA	1503	27057	UGUUGUACUUAUUGUACU	3154
27057	AGAUGUUAUUAUUGUUA	1504	27057	AGAUGUUAUUAUUGUUA	1504	27075	UCAACAAGAUUAAACAUUC	3155
27075	ACUCCAGGUUAACAUAAGC	1505	27075	ACUCCAGGUUAACAUAAGC	1505	27093	GCUAUUGUAACCGGGAAGU	3156
27093	CAGAGAUUAUUAUUAU	1506	27093	CAGAGAUUAUUAUUAU	1506	27111	AUGAUAUUAUUAUUAU	3157

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27111	UUUAGAGGACUUUCAGGAU	1507	27111	UUUAGAGGACUUUCAGGAU	1507	27129	AUCCUGAAAGUCCUCAUAA	3158
27129	UUGCUAUUUGGAUUCUUGA	1508	27129	UUGCUAUUUGGAUUCUUGA	1508	27147	UCAAGAUUCCAAUAGCAA	3159
27147	ACGUUAUUAAGUUCAAU	1509	27147	ACGUUAUUAAGUUCAAU	1509	27165	AUUGAACUUUAUUAACGU	3160
27165	UUGUAGACAAUUAUUA	1510	27165	UUGUAGACAAUUAUUA	1510	27183	UUAAUAAUUGUCUCACUA	3161
27183	AGCCUCUAAUUAAGAA	1511	27183	AGCCUCUAAUUAAGAA	1511	27201	UUUUCUUUAGUUAAGGCU	3162
27201	AUUUUCGGAGUUAUGA	1512	27201	AUUUUCGGAGUUAUGA	1512	27219	UCAUCUAAUCCGGAUUAU	3163
27219	UUGAAGAAUUAUGGAGU	1513	27219	UUGAAGAAUUAUGGAGU	1513	27237	AACUCCAAUAGGUUUCU	3164
27237	UAGAUUAUCCAAUUAACGA	1514	27237	UAGAUUAUCCAAUUAACGA	1514	27255	UCGUUUUAUUGGAUUAU	3165
27255	AACAUUAAUUAUUCUCU	1515	27255	AACAUUAAUUAUUCUCU	1515	27273	AGAGAUUAUUAUUAUGUU	3166
27273	UUCUGACAUUUAUUGUAU	1516	27273	UUCUGACAUUUAUUGUAU	1516	27291	AUACAAUUAUUGUCAGAA	3167
27291	UUUACAUUUGGAGCUAU	1517	27291	UUUACAUUUGGAGCUAU	1517	27309	AUAGCUGCAAGAUUAUA	3168
27309	UAUCAUUAUAGGAGUG	1518	27309	UAUCAUUAUAGGAGUG	1518	27327	CACACUCCUUAUAGUGUA	3169
27327	GUUAGAGUACGAGUAC	1519	27327	GUUAGAGUACGAGUAC	1519	27345	GUACAGUUGUACGUAAC	3170
27345	CUACUAAUAAUCCUUGCC	1520	27345	CUACUAAUAAUCCUUGCC	1520	27363	GGCAAGGUUUUAUUAUG	3171
27363	CCAUCAGGAACAUACGAGG	1521	27363	CCAUCAGGAACAUACGAGG	1521	27381	CCUUGAUUUGUCCUAGUG	3172
27381	GGCAUUAUCCAUUUCACC	1522	27381	GGCAUUAUCCAUUUCACC	1522	27399	GGUGAAUUGGUUAUUGCC	3173
27399	CCUUCUGGACAAUUAU	1523	27399	CCUUCUGGACAAUUAU	1523	27417	AUUUUAUUGUCAGCAAGG	3174
27417	UUUGCACUAAUUGCACUA	1524	27417	UUUGCACUAAUUGCACUA	1524	27435	UAGUGCAAGUUAUGGCAAA	3175
27435	AGCACACAUUUGCUUUUG	1525	27435	AGCACACAUUUGCUUUUG	1525	27453	CAAAAGCAAUGUGUGCU	3176
27453	GUUGUGGACGAGUACUC	1526	27453	GUUGUGGACGAGUACUC	1526	27471	GAGUACCGUACGACAAAGC	3177
27471	CGACUACCUUACGAGUC	1527	27471	CGACUACCUUACGAGUC	1527	27489	GCAGCAGUAGGUUAUGUCG	3178
27489	CGUGCAAGUACAGUUCAC	1528	27489	CGUGCAAGUACAGUUCAC	1528	27507	GUGAAUUGUUAUGGACG	3179
27507	CCAAACUUUUAUUAUGAC	1529	27507	CCAAACUUUUAUUAUGAC	1529	27525	GUCUGAUGAAAGUUUUGG	3180
27525	CAAGAGGAGUUAACAAG	1530	27525	CAAGAGGAGUUAACAAG	1530	27543	CUUUGUAGAACCUUUCUUG	3181
27543	GAGCUCUACUCGCCAUUU	1531	27543	GAGCUCUACUCGCCAUUU	1531	27561	AAAGUGGCGGUAAGAGCUC	3182
27561	UUUCUUAUUGUUGGUCUC	1532	27561	UUUCUUAUUGUUGGUCUC	1532	27579	GAGCAGCAACAUAUGAGAA	3183
27579	CUAGUAAUUAUUAUUAU	1533	27579	CUAGUAAUUAUUAUUAU	1533	27597	AAAGUAAUUAUUAUUAU	3184
27597	UGCUUACCAUUAAGAGAA	1534	27597	UGCUUACCAUUAAGAGAA	1534	27615	UUCUCUUAUUGGUAAGCA	3185
27615	AAGACAGAAUUAUUAUUA	1535	27615	AAGACAGAAUUAUUAUUA	1535	27633	AGCUCAUUUAUUGUUCU	3186
27633	UCACUUUAUUAUUAUUA	1536	27633	UCACUUUAUUAUUAUUA	1536	27651	UAGAGUCAAUUAUUAUGA	3187
27651	AUUUGUGCUUUUAUUAU	1537	27651	AUUUGUGCUUUUAUUAU	1537	27669	AAGGCUAAUUAUUAUUA	3188
27669	UUUGCUUUUAUUAUUAU	1538	27669	UUUGCUUUUAUUAUUAU	1538	27687	AAACAAAGGAUUAUUAU	3189
27687	UAAUUAUUAUUAUUAU	1539	27687	UAAUUAUUAUUAUUAU	1539	27705	AUAUUAUUAUUAUUAU	3190
27705	UUUGGUUUUAUUAUUAU	1540	27705	UUUGGUUUUAUUAUUAU	1540	27723	AUUUCGAGUAAUUAUUA	3191
27723	UCCAGGAUUAUUAUUAU	1541	27723	UCCAGGAUUAUUAUUAU	1541	27741	GGUUCUUAUUAUUAUUA	3192
27741	CUUGUACCAAGUUAUUA	1542	27741	CUUGUACCAAGUUAUUA	1542	27759	GUUUAUUAUUAUUAUUA	3193
27759	CGAACAUGAAUUAUUAU	1543	27759	CGAACAUGAAUUAUUAU	1543	27777	AUGAGAAGUUAUUAUUA	3194
27777	UUGUUUUAUUAUUAUUA	1544	27777	UUGUUUUAUUAUUAUUA	1544	27795	GAUAUUAUUAUUAUUA	3195
27795	CUCUAGUUAUUAUUAU	1545	27795	CUCUAGUUAUUAUUAU	1545	27813	CAUAUUAUUAUUAUUA	3196
27813	GCACUGUUAUUAUUAU	1546	27813	GCACUGUUAUUAUUAU	1546	27831	CAGCGUUAUUAUUAUUA	3197
27831	GUGCAUUAUUAUUAUUA	1547	27831	GUGCAUUAUUAUUAUUA	1547	27849	UGAGGUUAUUAUUAUUA	3198
27849	AUGUGCUUAUUAUUAU	1548	27849	AUGUGCUUAUUAUUAU	1548	27867	CAAGGAUUAUUAUUAU	3199

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27867	GUAGGUACAAACUAGGG	1549	27867	GUAGGUACAAACUAGGG	1549	27885	CCUAGUGUUGUACCUUAC	3200
27885	GGUAAUACUUAUAGCACUG	1550	27885	GGUAAUACUUAUAGCACUG	1550	27903	CAGUGCUAAAGUUAUAGC	3201
27903	GUUGGUUUUGUCUUAUAG	1551	27903	GUUGGUUUUGUCUUAUAG	1551	27921	CUAAGGCAAAAGCCAAAGC	3202
27921	GGAAAGUUUUAACCUUUG	1552	27921	GGAAAGUUUUAACCUUUG	1552	27939	GAAAGGUAAACCUUUG	3203
27939	CAUAGAUGGCACAUUAG	1553	27939	CAUAGAUGGCACAUUAG	1553	27957	CCAUAGUGGCCAUUAG	3204
27957	GUUCAAACUAGCACCUA	1554	27957	GUUCAAACUAGCACCUA	1554	27975	UAGGUGUGCAUUGUAGAC	3205
27975	AUUGUUAUUAACUAGC	1555	27975	AUUGUUAUUAACUAGC	1555	27993	GACAGUUGAUAGUAAAUU	3206
27993	CAAGAUCAGCUGGUGUG	1556	27993	CAAGAUCAGCUGGUGUG	1556	28011	CACCAACGUGGUGUUG	3207
28011	GGCUUAUAGCUGGUGU	1557	28011	GGCUUAUAGCUGGUGU	1557	28029	AACACCUAGCUAAGCGC	3208
28029	UGGUACCUUAUAGGUG	1558	28029	UGGUACCUUAUAGGUG	1558	28047	GACCUUAUAGGUGUAGCA	3209
28047	CACCAACUGCUGCAUUA	1559	28047	CACCAACUGCUGCAUUA	1559	28065	UAAUAGCAGCAGUUGGUG	3210
28065	AGAGACGUACUUGUUGU	1560	28065	AGAGACGUACUUGUUGU	1560	28083	AAACAACAGUACGUCUCU	3211
28083	UAAAUAAACGAAAUU	1561	28083	UAAAUAAACGAAAUU	1561	28101	AUUUUGUUGUUAUUA	3212
28101	UAAAUUGUCUGAUUAGGA	1562	28101	UAAAUUGUCUGAUUAGGA	1562	28119	UCCAUUAUCAGAUUUUA	3213
28119	ACCCAAUCAAACCAACGU	1563	28119	ACCCAAUCAAACCAACGU	1563	28137	ACGUUGUUGUUAUUGGGU	3214
28137	UAGUGCCCGCCGUAUACA	1564	28137	UAGUGCCCGCCGUAUACA	1564	28155	UGUAAUGCGGGGCGACUA	3215
28155	AUUUGGUGACCCACAGAU	1565	28155	AUUUGGUGACCCACAGAU	1565	28173	AUCUGUGGUGCCCAAAU	3216
28173	UUAACUGGACAAUACCCAG	1566	28173	UUAACUGGACAAUACCCAG	1566	28191	CUGGUUAUUGUCAGUUGAA	3217
28191	GAUUGGAGGACGAAUUGG	1567	28191	GAUUGGAGGACGAAUUGG	1567	28209	CCAUUGCGUCCUCCAUUC	3218
28209	GGCAAGGCCAAACAGCGC	1568	28209	GGCAAGGCCAAACAGCGC	1568	28227	GGCGUUAUUGGCUUGCC	3219
28227	CGACCCCAAGGUUAUACCC	1569	28227	CGACCCCAAGGUUAUACCC	1569	28245	GGUAAACCUUGGGGUGCG	3220
28245	CAAAUUAUUGGCUUUG	1570	28245	CAAAUUAUUGGCUUUG	1570	28263	CCAGACGCGCAUUAUUG	3221
28263	GUUCACAGCUCACUCAG	1571	28263	GUUCACAGCUCACUCAG	1571	28281	CUGAGUGAGAGCUGUGAAC	3222
28281	GCAUGGCAAGGAGGAU	1572	28281	GCAUGGCAAGGAGGAU	1572	28299	AAGUCCUCCUUGCCAUUGC	3223
28299	UAGAUUCCUCCGAGGCGAG	1573	28299	UAGAUUCCUCCGAGGCGAG	1573	28317	CUGGCCUCGAGGGAUUA	3224
28317	GGGCUUCCAAUACACACC	1574	28317	GGGCUUCCAAUACACACC	1574	28335	GGUUGUAGUUGGAACGCC	3225
28335	CAUAGUGGUCACAGUAGC	1575	28335	CAUAGUGGUCACAGUAGC	1575	28353	GUCUUGGAGGCCACUUAUG	3226
28353	CCAAUUGGCUUACCCGA	1576	28353	CCAAUUGGCUUACCCGA	1576	28371	UCGGUAGUAGCCAAUUAUG	3227
28371	AAGAGCUACCCGAGGAGU	1577	28371	AAGAGCUACCCGAGGAGU	1577	28389	AACUCGCGGGUAGCUCU	3228
28389	UCGUGGUGGACGGCAA	1578	28389	UCGUGGUGGACGGCAA	1578	28407	UUUCCCGUACCCACACGA	3229
28407	AUUGAAAGAGCUCAGCC	1579	28407	AUUGAAAGAGCUCAGCC	1579	28425	GGGGUGAGCUCUUAUUA	3230
28425	CAGUUGGUACUUAUUA	1580	28425	CAGUUGGUACUUAUUA	1580	28443	GUAAUAGAAAGUACCAUC	3231
28443	CCUAGGAACUGGCCAGAA	1581	28443	CCUAGGAACUGGCCAGAA	1581	28461	UUCUGGGCCAGUCCUAGG	3232
28461	AGCUUACUCCUACCGC	1582	28461	AGCUUACUCCUACCGC	1582	28479	GCGUAGGGAAGUGAAGCU	3233
28479	CGCUAACAAGAGGCAUC	1583	28479	CGCUAACAAGAGGCAUC	1583	28497	GAUGCCUUCUUAUAGCG	3234
28497	CGUUGGUUGCAACUGAG	1584	28497	CGUUGGUUGCAACUGAG	1584	28515	CUCAGUUGCAACCCUAGC	3235
28515	GGGAGCCUUGAAUACACC	1585	28515	GGGAGCCUUGAAUACACC	1585	28533	GGGUGUUAUCAAAGGCUCC	3236
28533	CAAAGACCAUUGGCACC	1586	28533	CAAAGACCAUUGGCACC	1586	28551	GGUGCCAAUGUGGCUUUG	3237
28551	CGCACAUCUUAUAAUUA	1587	28551	CGCACAUCUUAUAAUUA	1587	28569	AUUGUUAUUAAGGAUUGCGG	3238
28569	UGUGGCCACCGUGUACAA	1588	28569	UGUGGCCACCGUGUACAA	1588	28587	UUGUAGCACGGUGGCGCA	3239
28587	ACUUCUCAAGGAACA	1589	28587	ACUUCUCAAGGAACA	1589	28605	UGUUGUCCUUGAGGAAGU	3240
28605	AUUGCCAAAAGGCUUAC	1590	28605	AUUGCCAAAAGGCUUAC	1590	28623	GUAGAAAGCCUUUUGGCAU	3241

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28623	CGCAGAGGGAAGCAGAGGC	1591	28623	CGCAGAGGGAAGCAGAGGC	1591	28641	GCUCUCGCUUCCUCUGCG	3242
28641	CGCAGAGGGAAGCUCUUCU	1592	28641	CGCAGAGGGAAGCUCUUCU	1592	28659	AGCAGAGGCUUAGCUGCGG	3243
28659	UCGCUUCCUAUCAGUAGU	1593	28659	UCGCUUCCUAUCAGUAGU	1593	28677	ACUAGUGUAGAGAGCGA	3244
28677	UCGCGGUAUUAAGAAU	1594	28677	UCGCGGUAUUAAGAAU	1594	28695	AUUCUUGAAUACCGCGA	3245
28695	UUAACUCCUGGAGCAGU	1595	28695	UUAACUCCUGGAGCAGU	1595	28713	ACUGCUGCAGGAGUUGAA	3246
28713	UAGGGGAAUUCUUCUGCU	1596	28713	UAGGGGAAUUCUUCUGCU	1596	28731	AGCAGGAGAAUUCUCCUA	3247
28731	UCGAAUGGCUAGCGGAGU	1597	28731	UCGAAUGGCUAGCGGAGU	1597	28749	ACUCCGCUAGCCAUUCGA	3248
28749	UGGUAACUGCCUUGCGG	1598	28749	UGGUAACUGCCUUGCGG	1598	28767	CGCAGGCGCAUUCACCA	3249
28767	GUUUGUGUGUAGACAGA	1599	28767	GUUUGUGUGUAGACAGA	1599	28785	UCUGCUAGCAGCAUAGC	3250
28785	AUUGAACGAGUAGAGC	1600	28785	AUUGAACGAGUAGAGC	1600	28803	GCUCUCAAGCUGGUUCAAU	3251
28803	CAAAGUUCUGGUAAGGC	1601	28803	CAAAGUUCUGGUAAGGC	1601	28821	GCUIUJACCAGAAACUUG	3252
28821	CCAACAACAAAGGCCAA	1602	28821	CCAACAACAAAGGCCAA	1602	28839	UUGGCCUUGUUGUUGG	3253
28839	AACUGACACUAAGAAUCU	1603	28839	AACUGACACUAAGAAUCU	1603	28857	AGAUUCUJAGUGACAGUU	3254
28857	UGCUGCUGAGGCAUCUAA	1604	28857	UGCUGCUGAGGCAUCUAA	1604	28875	UUUAGAUGCCUCGACAGCA	3255
28875	AAAGCCUGGCCAAACGCU	1605	28875	AAAGCCUGGCCAAACGCU	1605	28893	ACGUUUUUGGCGAGGCUUU	3256
28893	UACUGCCACAAACAGUAC	1606	28893	UACUGCCACAAACAGUAC	1606	28911	GUACUUGUUUUGGCGAGUA	3257
28911	CAACGUCACUAAGCAUUU	1607	28911	CAACGUCACUAAGCAUUU	1607	28929	AAUUGCUAGUGAGCGUUG	3258
28929	UGGGAGACGUGUCCAGAA	1608	28929	UGGGAGACGUGUCCAGAA	1608	28947	UUCUGGACCACGUCUCCCA	3259
28947	ACAAACCCAAAGAAUUC	1609	28947	ACAAACCCAAAGAAUUC	1609	28965	GAAAUUCCUUGGGUUGU	3260
28965	CGGGAGCAAGACCUAAC	1610	28965	CGGGAGCAAGACCUAAC	1610	28983	GAUAGGCUUUGGUCUCCG	3261
28983	CAGACAAGGACUGAUUAC	1611	28983	CAGACAAGGACUGAUUAC	1611	29001	GUAAUGCUUCCUUGUCUG	3262
29001	CAACAAGGCGCAAAU	1612	29001	CAACAAGGCGCAAAU	1612	29019	AAUUGCGGCAUUGUUG	3263
29019	UGCACAUUUGCUCCAAU	1613	29019	UGCACAUUUGCUCCAAU	1613	29037	ACUUGGAGCAAAUUGUGCA	3264
29037	UGCCUCUGCAUUCUUGGA	1614	29037	UGCCUCUGCAUUCUUGGA	1614	29055	UCCAAAGAAUGCAGAGGCA	3265
29055	AUUGUCACGCUUUGGCAUG	1615	29055	AUUGUCACGCUUUGGCAUG	1615	29073	CAUGCCAAUGCGUGACAUU	3266
29073	GGAAGUCACACUUCGGGA	1616	29073	GGAAGUCACACUUCGGGA	1616	29091	UCCCGAAGGUGUGACUUC	3267
29091	AACAUGGCUAGCUUACAU	1617	29091	AACAUGGCUAGCUUACAU	1617	29109	AUGAAAGUCAGCCAUUGU	3268
29109	UGGAGCCAUUAAUUGGAU	1618	29109	UGGAGCCAUUAAUUGGAU	1618	29127	AUCCAAUUUAUUGGCUCCA	3269
29127	UGACAAAGAUCCACAAUUC	1619	29127	UGACAAAGAUCCACAAUUC	1619	29145	GAUUGUGGCUUUGUUGCA	3270
29145	CAAAGACAAGCUCUACUG	1620	29145	CAAAGACAAGCUCUACUG	1620	29163	CAGUAGACGCUUUGUUG	3271
29163	GCUGAACAGCAUUGAC	1621	29163	GCUGAACAGCAUUGAC	1621	29181	GUCAAUGUGCUUUGUAGC	3272
29181	CGCAUACAAACAUUCCCA	1622	29181	CGCAUACAAACAUUCCCA	1622	29199	UGGGAUUGUUUUGUUGCG	3273
29199	ACCAACAGAGCCUAAAG	1623	29199	ACCAACAGAGCCUAAAG	1623	29217	CUUUUAGGCUUUGUUGU	3274
29217	GGACAAAAGAAAGACU	1624	29217	GGACAAAAGAAAGACU	1624	29235	AGUCUUUUUUCUUUUGUCC	3275
29235	UGAUGAAGCUCAGCCUUG	1625	29235	UGAUGAAGCUCAGCCUUG	1625	29253	CAAGGCUAGGCUUUCAUCA	3276
29253	GCCGAGAGACAAAGAAAG	1626	29253	GCCGAGAGACAAAGAAAG	1626	29271	CUUCUUUUUGUCUCGCGG	3277
29271	GCAGCCACUGUGACUUCU	1627	29271	GCAGCCACUGUGACUUCU	1627	29289	AAGAGUCACAGUGGCGUC	3278
29289	UCUUCUGCGGUGACAU	1628	29289	UCUUCUGCGGUGACAU	1628	29307	CAUGCAGCCGCGAGGAAGA	3279
29307	GAUGAUUUUCCAGACAA	1629	29307	GAUGAUUUUCCAGACAA	1629	29325	UUGCUGGAGAAUUCAUCC	3280
29325	ACUCAAUUUCCAGAGU	1630	29325	ACUCAAUUUCCAGAGU	1630	29343	ACUCUAGGAAUUGUAGAU	3281
29343	UGGAGCUUCUGUGAUUCA	1631	29343	UGGAGCUUCUGUGAUUCA	1631	29361	UGAAUCAGCAGAGGCUCCA	3282
29361	AACUCAGGCAUAAACACUC	1632	29361	AACUCAGGCAUAAACACUC	1632	29379	GAGUGUUUAUGCCUGAGUU	3283

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29379	CAUGAUGACCACACAAGGC	1633	29379	CAUGAUGACCACACAAGGC	1633	29397	GCCUUGUGGGUCAUCUG	3284
29397	CAGAUGGGCUAUGAAACG	1634	29397	CAGAUGGGCUAUGAAACG	1634	29415	CGUUUACAUGCCCAUCUG	3285
29415	GUUUUGCAUUCGCUUA	1635	29415	GUUUUGCAUUCGCUUA	1635	29433	UAAACGGAAUUGCGAAAC	3286
29433	ACGAUACAUGUCUACUCU	1636	29433	ACGAUACAUGUCUACUCU	1636	29451	AGAGUAGACUAUGUAUCGU	3287
29451	UUGUGCAGAAUGAAUUCUC	1637	29451	UUGUGCAGAAUGAAUUCUC	1637	29469	GAGAAUACAUCUGACAA	3288
29469	CGUAAACAAACGACCAAG	1638	29469	CGUAAACAAACGACCAAG	1638	29487	CUUGUGCUGUUUAGUUACG	3289
29487	GUAGGUUUAGUUAACUUA	1639	29487	GUAGGUUUAGUUAACUUA	1639	29505	UAAAGUUAAACAAACCUAC	3290
29505	AAUCUCACAUGCAUUCUU	1640	29505	AAUCUCACAUGCAUUCUU	1640	29523	AAGAUUGCUAUGUGAGAUU	3291
29523	UUAUCAAUGUGUACAUAU	1641	29523	UUAUCAAUGUGUACAUAU	1641	29541	AAUGUUACACAUGAUUAA	3292
29541	UAGGGAGGACUUGAAAGAG	1642	29541	UAGGGAGGACUUGAAAGAG	1642	29559	CUCUUACAAGUCCUCCUA	3293
29559	GCCACCACAUUUUCAUCGA	1643	29559	GCCACCACAUUUUCAUCGA	1643	29577	UCGAUGAAAUGUGGUGGC	3294
29577	AGGCCACGCGGAGUACGAU	1644	29577	AGGCCACGCGGAGUACGAU	1644	29595	AUCGUACUCCGCGUGGCCU	3295
29595	UCGAGGGUACAGUGAAUAA	1645	29595	UCGAGGGUACAGUGAAUAA	1645	29613	UUUUUACACUGUACCCUGA	3296
29613	AUGCUAGGGAGAGCUGCCU	1646	29613	AUGCUAGGGAGAGCUGCCU	1646	29631	AGGCAGCUCUCCCUAGCAU	3297
29631	UAUUGGAAGAGCCCUAAU	1647	29631	UAUUGGAAGAGCCCUAAU	1647	29649	AUUAGGCUCUUCUCCAUUA	3298
29649	UGUGUAAAUAUUUUUAG	1648	29649	UGUGUAAAUAUUUUUAG	1648	29667	CUAAAUAUUUUUACACA	3299
29667	GUAGUGCUAUCCCAUGUG	1649	29667	GUAGUGCUAUCCCAUGUG	1649	29685	CACAUUGGGAUAGCACUAC	3300
29685	GAUUUUAAUAGCUUCUAG	1650	29685	GAUUUUAAUAGCUUCUAG	1650	29703	CUAAGAAGCUAUUAAAUC	3301
29703	GGAGAAUGACAAAAAAA	1651	29703	GGAGAAUGACAAAAAAA	1651	29721	UUUUUUUUUGUCAUUGCC	3302

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence of the lower sequence is optionally complementary to a portion of the target sequence. The overhang can comprise the general structure B, BNN, NN, BNsN, or NsN, where B stands for any terminal cap moiety, N stands for any nucleotide (e.g., thymidine) and s stands for phosphorothioate or other internucleotide linkage as described herein (e.g. internucleotide linkage having Formula I). The upper sequence is also referred to as the sense strand, whereas the lower sequence is also referred to as the antisense strand. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII or any combination thereof (see for example chemical modifications as shown in Table V herein).

Target Pos	Target	SeqID	RPI#	Aliases	Sequence	SeqID
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1657U21 siRNA sense	AAUGAAGAGGUGGCCAUCATT	3311
1164	UGUUGCAUCCACACAGGAGUGUA	3304		SARS:1168U21 siRNA sense	UUUGCAUCCACACAGGAGUUTT	3312
2381	CUCAAGCAAGGACUUAACCGU	3305		SARS:2383U21 siRNA sense	CAAGCAAGGACUUAACCTT	3313
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA sense	GUGUAAAUGGCCUCAUGCUUTT	3314
26572	UUUGUGCUUGCUGUGUCUACAG	3307		SARS:26574U21 siRNA sense	UUUGCUUGCUGUGUCUACATT	3315
26790	ACUUGCAUUGGUGCUGUGAUCU	3308		SARS:26792U21 siRNA sense	UUUGCAUUGGUGCUGUGAUUTT	3316
28786	UUGAACACGCUUGAGAGCAAGU	3309		SARS:28788U21 siRNA sense	GAACACGCUUGAGAGCAAAATT	3317
26529	GCUUGUUUCCUCUGGCCUCUUGU	3310		SARS:26531U21 siRNA sense	UUUUUUUCCUCUGGCCUCUUTT	3318
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) antisense	UGAUGGCAACCUUCUUAUUTT	3319
1164	UGUUGCAUCCACACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) antisense	CACUCCUGUGGAGAUUGCAATT	3320
2381	CUCAAGCAAGGACUUAACCGU	3305		SARS:2401L21 siRNA (2383C) antisense	GGUAAAUGUCCUUGCUUUGUTT	3321
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) antisense	AGCAUGAGGCCAUUUACACATT	3322
26572	UUUGUGCUUGCUGUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) antisense	GUAGACAGCAGCAAGCACATT	3323
26790	ACUUGCAUUGGUGCUGUGAUCU	3308		SARS:26810L21 siRNA (26792C) antisense	AUCACAGCACCACAAUGACAATT	3324
28786	UUGAACCAAGCUUGAGAGCAAGU	3309		SARS:28806L21 siRNA (28788C) antisense	UUUGCUCUCAAGCUGGUUUCTT	3325
26529	GCUUGUUUCCUCUGGCCUCUUGU	3310		SARS:26549L21 siRNA (26531C) antisense	AAGAGCCAGAGGAAAAACAATT	3326
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1657U21 siRNA stab04 sense	B AAUGAAGAGGUUGCCAUCAATT B	3327
1164	UGUUGCAUCCACACAGGAGUGUA	3304		SARS:1168U21 siRNA stab04 sense	B UUUGCAUCCACACAGGAGUUTT B	3328
2381	CUCAAGCAAGGACUUAACCGU	3305		SARS:2383U21 siRNA stab04 sense	B CAAAGCAAGGAGACUUUAACCTT B	3329
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA stab04 sense	B GUUGUAAAUGGCCUCAUGCUUTT B	3330
26572	UUUGUGCUUGCUGUGUCUACAG	3307		SARS:26574U21 siRNA stab04 sense	B UUUGUuuUGGUGCUUGCAUUTT B	3331
26790	ACUUGCAUUGGUGCUGUGAUCU	3308		SARS:26792U21 siRNA stab04 sense	B UUUGCAUuuUGGUGCUUGCAUUTT B	3332
28786	UUGAACCAAGCUUGAGAGCAAGU	3309		SARS:28788U21 siRNA stab04 sense	B GAAACCAAGUUUGAGAGCAAAATT B	3333
26529	GCUUGUUUCCUCUGGCCUCUUGU	3310		SARS:26531U21 siRNA stab04 sense	B UUUGUUUUUCCUCUGGCCUCUUTT B	3334
1655	UGAUGAAGAGGUGGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) stab05 antisense	UGAUGGCAACCUUCUUAUUTsT	3335
1164	UGUUGCAUCCACACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab05 antisense	CACUCCUGUGGAGAUUGCAATsT	3336

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2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2401L21 siRNA (2383C) stab05 antisense	GGUAAAAGuccuuGcuuuGTsT	3337
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306	SARS:2618L21 siRNA (2600C) stab05 antisense	AGcAuGAGGccAuuuAcAcTsT	3338
26572	UUUGUGCUUGCUGCUGUCUACAG	3307	SARS:26592L21 siRNA (26574C) stab05 antisense	GUAGAcAGcAGcAAAGcAcATsT	3339
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26810L21 siRNA (26792C) stab05 antisense	AucAcAGcAcAAuGAcAAATsT	3340
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28806L21 siRNA (28788C) stab05 antisense	uuuGcuucAAAGcuGGuucTsT	3341
26529	GCUUUUUUUCCUCUGGCCUCUUGU	3310	SARS:26549L21 siRNA (26531C) stab05 antisense	AAGAGccAGAGGAAAcAAATsT	3342
1655	UGAAUGAAGAGGUUGCCAUCAU	3303	SARS:1657U21 siRNA stab07 sense	B AAUGAAGAGGGuuGccAuATT B	3343
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA stab07 sense	B uuGcAuucuccAcAGGAGuGTT B	3344
2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2383U21 siRNA stab07 sense	B CAAAGCAAGGGAcAuuuAccTT B	3345
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306	SARS:2600U21 siRNA stab07 sense	B GuGuAAuGGccuAuGcuTT B	3346
26572	UUUGUCUUGCUGCUGUCUACAG	3307	SARS:26574U21 siRNA stab07 sense	B uGuGcuuGcuGcuGcuAcTT B	3347
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26792U21 siRNA stab07 sense	B uuGucAuuuGGuGcuGuGauTT B	3348
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28788U21 siRNA stab07 sense	B GAAccAGcuuGAGAGcAAATT B	3349
26529	GCUUUUUUUCCUCUGGCCUCUUGU	3310	SARS:26531U21 siRNA stab07 sense	B uuGuuuuccuGcGcuuuTT B	3350
1655	UGAAUGAAGAGGUUGCCAUCAU	3303	SARS:1675L21 siRNA (1657C) stab11 antisense	UGAuGGcAAccuucAuuuTsT	3351
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1184L21 siRNA (1166C) stab11 antisense	cAcuccuGuGGAGAuGcAAATsT	3352
2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2401L21 siRNA (2383C) stab11 antisense	GGUAAAAGuccuuGcuuuGTsT	3353
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306	SARS:2618L21 siRNA (2600C) stab11 antisense	AGcAuGAGGccAuuuAcAcTsT	3354
26572	UUUGUGCUUGCUGCUGUCUACAG	3307	SARS:26592L21 siRNA (26574C) stab11 antisense	GUAGAcAGcAGcAAAGcAcATsT	3355
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26810L21 siRNA (26792C) stab11 antisense	AucAcAGcAcAAuGAcAAATsT	3356
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28806L21 siRNA (28788C) stab11 antisense	uuuGcuucAAAGcuGGuucTsT	3357
26529	GCUUUUUUUCCUCUGGCCUCUUGU	3310	SARS:26549L21 siRNA (26531C) stab11 antisense	AAGAGccAGAGGAAAcAAATsT	3358
1655	UGAAUGAAGAGGUUGCCAUCAU	3303	SARS:1657U21 siRNA stab08 sense	AAUGAAGAGGGuuGccAuATTsT	3359
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA stab08 sense	uuGcAuucuccAcAGGAGuGTTsT	3360
2381	CUCAAAGCAAGGGACUUAUACCGU	3305	SARS:2383U21 siRNA stab08 sense	cAAAGcAAAGGGAcAuuuAccTsT	3361
2598	CUGUGUAAAUGGCCUCAUGCUCU	3306	SARS:2600U21 siRNA stab08 sense	GuGuAAAuGGccuAuGcuTsT	3362

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26572	UUUGUCUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA stab08 sense	uGuGcuuGcuGcuGucuAcTsT	3363
26780	ACUUGUCAUUGGUGCUGUGAUA	3308		SARS:26792U21 siRNA stab08 sense	uuGucAuuGGuGcuGUGAUtsT	3364
28786	UUGAACCCAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab08 sense	GAAccAGcuuGAGAGGcAAATsT	3365
26529	GCUUGUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA stab08 sense	uuGuuuuuccucuGGcucuTsT	3366
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) stab08 antisense	UGAuGGcAAccucuucAuuTsT	3367
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab08 antisense	cAcuccuGuGGAGAuGcAATsT	3368
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) stab08 antisense	GGuAAAAGucccuuGcuuGTsT	3369
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) stab08 antisense	AGcAuGAGGccAuuuAcAcTsT	3370
26572	UUUGUCUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) stab08 antisense	G <u>u</u> AGAcAGcAGcAAAGcAcTsT	3371
26790	ACUUGUCAUUGGUGCUGUGAUA	3308		SARS:26810L21 siRNA (26792C) stab08 antisense	AucAcAGcAc <u>cc</u> AuGAcAAATsT	3372
28786	UUGAACCCAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) stab08 antisense	uuuGcucucAAAGcuGGuucTsT	3373
26529	GCUUGUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) stab08 antisense	AAGAGccAGAGGAAAAcAAATsT	3374

Uppercase = ribonucleotide

u,c = 2'-deoxy-2'-fluoro U, C

A = 2'-O-methyl AdenosineG = 2'-O-methyl Guanosine

T = thymidine

B = inverted deoxy abasic

s = phosphorothioate linkage

A = deoxy Adenosine

G = deoxy Guanosine

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16"	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		Usually AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end -		Usually AS

CAP = any terminal cap, see for example Figure 10.

All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues

All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.

S = sense strand

AS = antisense strand

Table V

A. 2.5 μ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 μ L	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 μ L	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 μ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 μ L	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 μ L	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 μ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 μ L	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 μ L	45 sec	233 min	465 sec
Acetic Anhydride	655	124 μ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 μ L	5 sec	5 sec	5 sec
TCA	700	732 μ L	10 sec	10 sec	10 sec
Iodine	20.6	244 μ L	15 sec	15 sec	15 sec
Beaucage	7.7	232 μ L	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 μ mol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O- methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O- methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 μ L	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 μ L	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 μ L	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 μ L	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 μ L	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 μ L	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 μ L	NA	NA	NA

- 5
- Wait time does not include contact time during delivery.
 - Tandem synthesis utilizes double coupling of linker molecule

CLAIMS

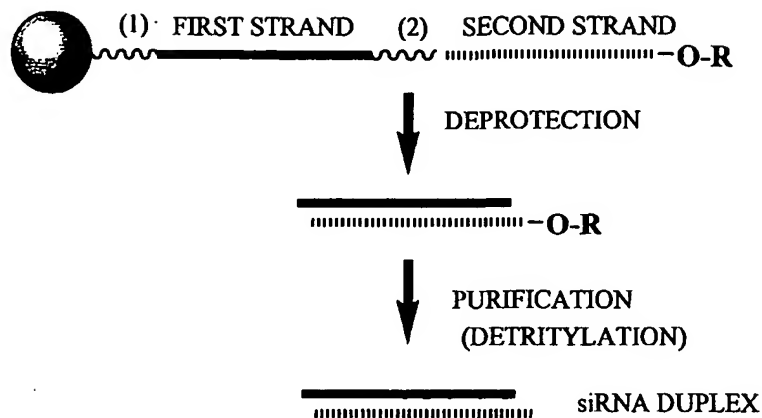
What we claim is:

1. A chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a severe acute respiratory syndrome (SARS) virus RNA via RNA interference, wherein:
 - a. each strand of said siNA molecule is about 19 to about 23 nucleotides in length;
 - b. one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said SARS virus RNA for the siNA molecule to direct cleavage of the SARS virus RNA via RNA interference; and
 - c. said siNA molecule does not require the presence of nucleotides having a 2'-hydroxy group for mediating RNA interference.
2. The siNA molecule of claim 1, wherein said siNA molecule comprises no ribonucleotides.
3. The siNA molecule of claim 1, wherein said siNA molecule comprises ribonucleotides.
4. The siNA molecule of claim 1, wherein one strand of said double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein a second strand of said double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of said SARS virus RNA.
5. The siNA molecule of claim 4, wherein each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand.
6. The siNA molecule of claim 1, wherein said siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein said siNA further comprises a sense region, wherein said sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of said SARS virus gene or a portion thereof.

7. The siNA molecule of claim 6, wherein said antisense region and said sense region comprises about 19 to about 23 nucleotides, and wherein said antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region.
- 5 8. The siNA molecule of claim 1, wherein said siNA molecule comprises a sense region and an antisense region, and wherein said antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS virus gene, or a portion thereof, and said sense region comprises a nucleotide sequence that is complementary to said antisense region.
- 10 9. The siNA molecule of claim 6, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region of said siNA molecule.
10. The siNA molecule of claim claim 6, wherein said sense region is connected to the antisense region via a linker molecule.
- 15 11. The siNA molecule of claim 10, wherein said linker molecule is a polynucleotide linker.
12. The siNA molecule of claim 10, wherein said linker molecule is a non-nucleotide linker.
13. The siNA molecule of claim 6, wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides.
- 20 14. The siNA molecule of claim 6, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides.
15. The siNA molecule of claim 6, wherein pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
- 25 16. The siNA molecule of claim 9, wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment comprising said sense region.
17. The siNA molecule of claim 16, wherein said terminal cap moiety is an inverted deoxy abasic moiety.
- 30 18. The siNA molecule of claim 6, wherein pyrimidine nucleotides of said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides

19. The siNA molecule of claim 6, wherein purine nucleotides of said antisense region are 2'-O-methyl purine nucleotides.
20. The siNA molecule of claim 6, wherein purine nucleotides present in said antisense region comprise 2'-deoxy- purine nucleotides.
- 5 21. The siNA molecule of claim 18, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.
22. The siNA molecule of claim 6, wherein said antisense region comprises a glyceryl modification at the 3' end of said antisense region.
23. The siNA molecule of claim 9, wherein each of the two fragments of said siNA
10 molecule comprise 21 nucleotides.
24. The siNA molecule of claim 23, wherein about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other
15 fragment of the siNA molecule.
25. The siNA molecule of claim 24, wherein each of the two 3' terminal nucleotides of each fragment of the siNA molecule are 2'-deoxy-pyrimidines.
26. The siNA molecule of claim 25, wherein said 2'-deoxy-pyrimidine is 2'-deoxy-thymidine.
- 20 27. The siNA molecule of claim 23, wherein all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule.
28. The siNA molecule of claim 23, wherein about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
25
29. The siNA molecule of claim 23, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
30. The siNA molecule of claim 9, wherein the 5'-end of the fragment comprising said
30 antisense region optionally includes a phosphate group.

31. A pharmaceutical composition comprising the siNA molecule of claim 1 in an acceptable carrier or diluent.

Figure 1

= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP

FOR EXAMPLE:

- DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

(2) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

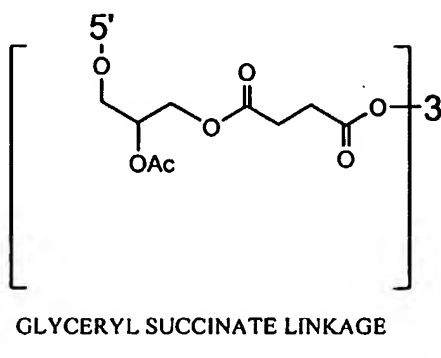
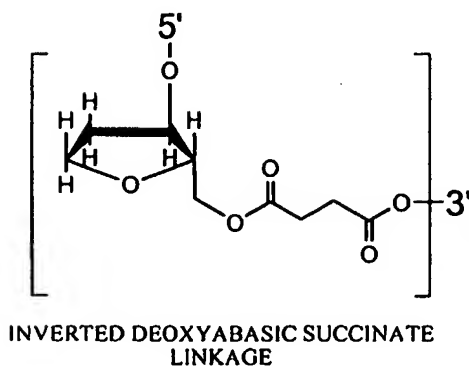


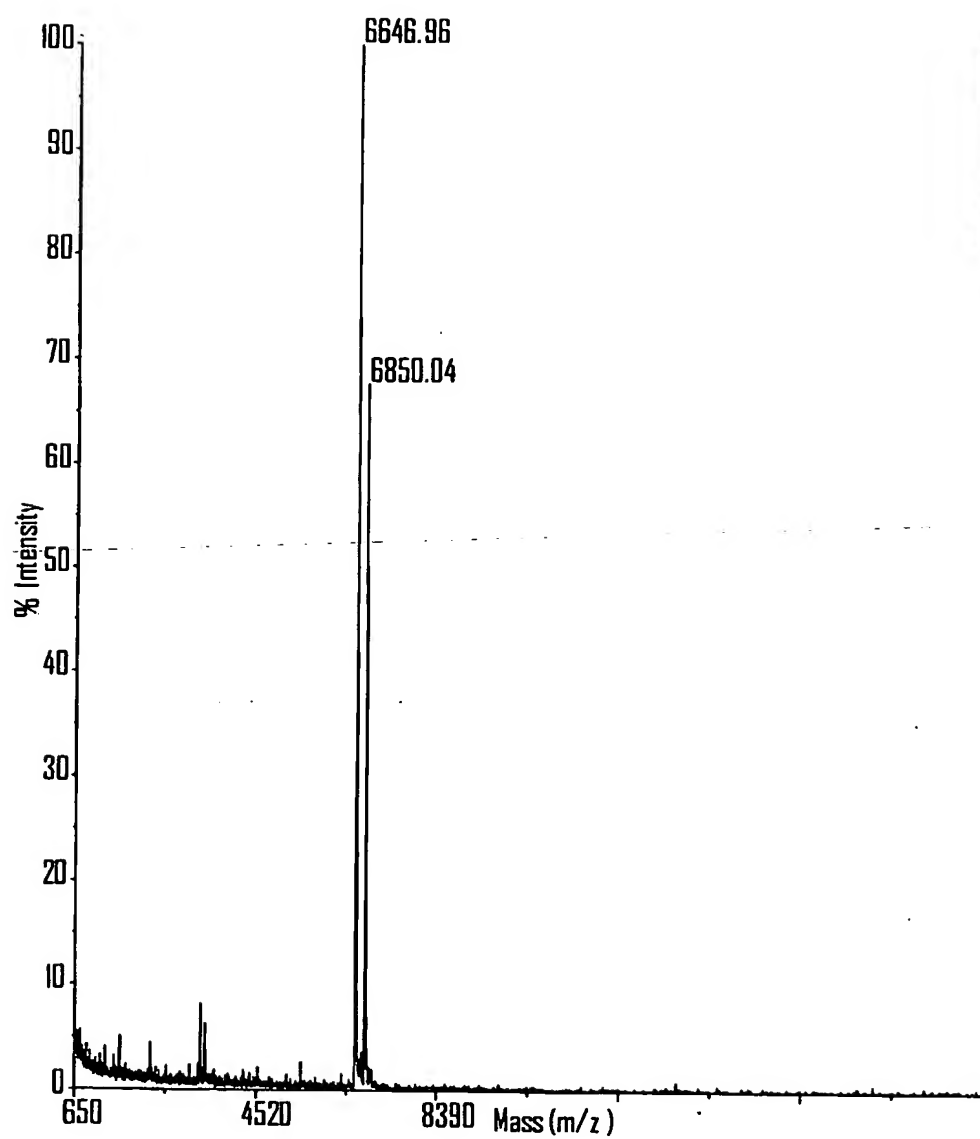
Figure 2

Figure 3

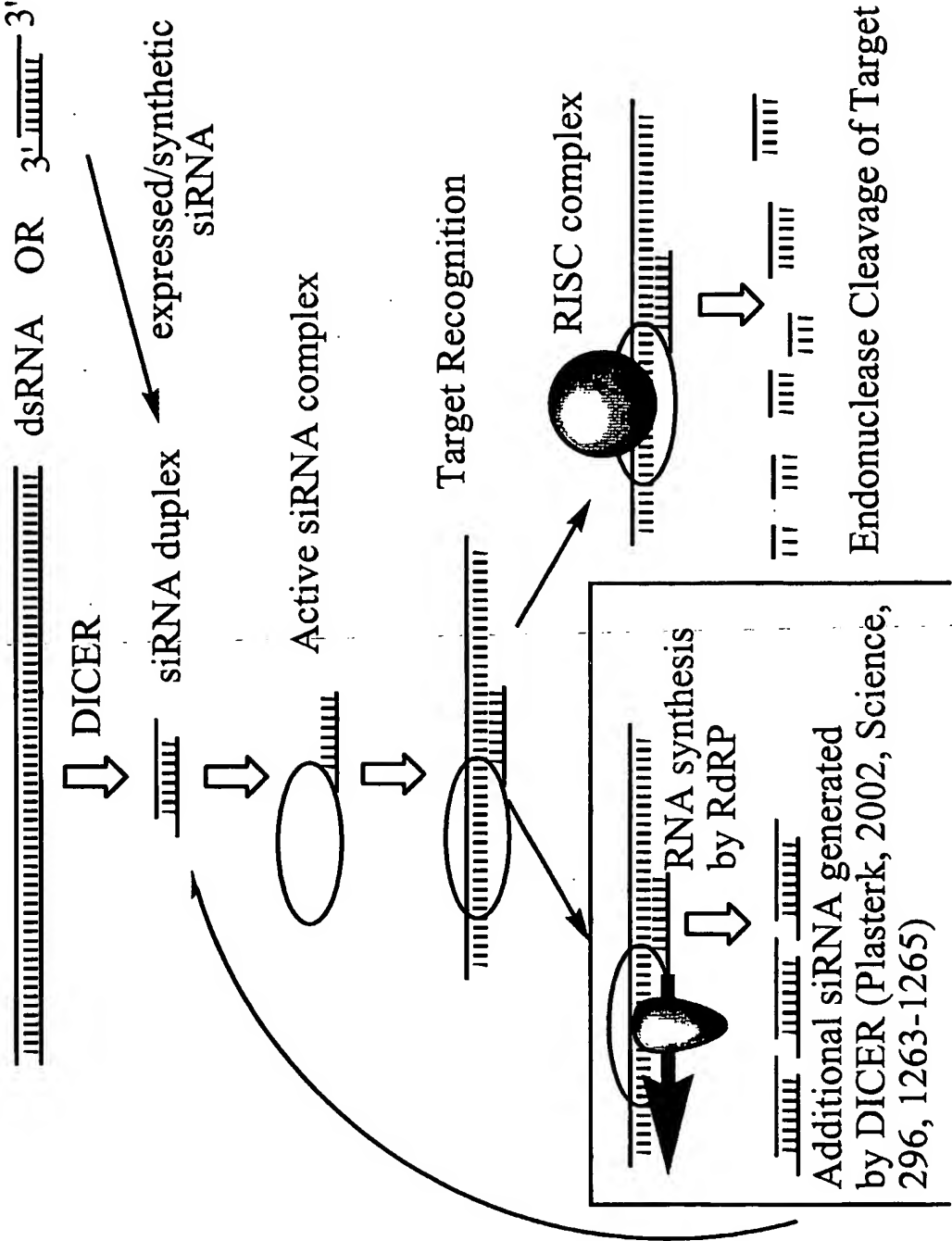
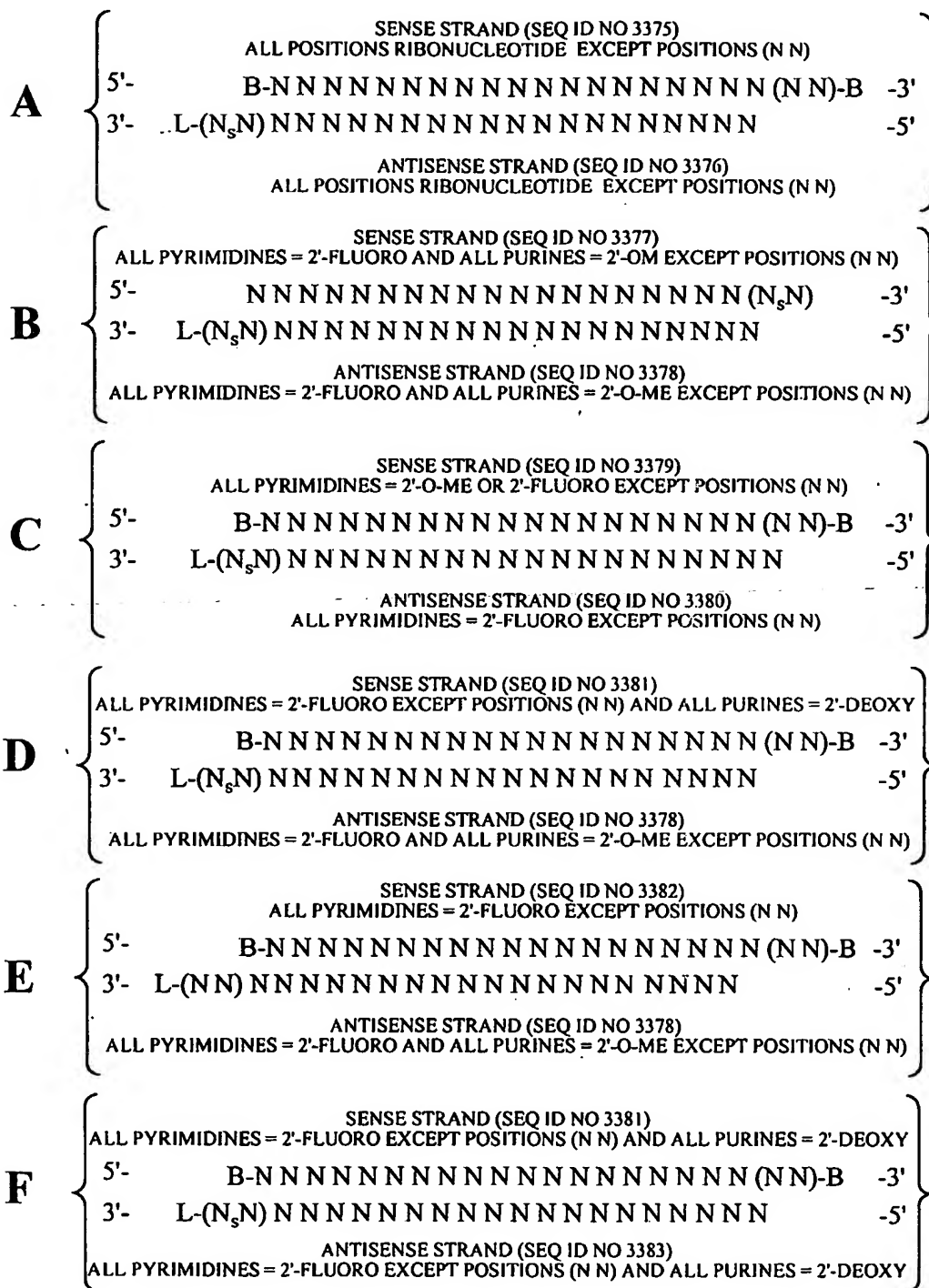


Figure 4



POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENTL = GLYCERYL or B THAT IS OPTIONALLY PRESENTS = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

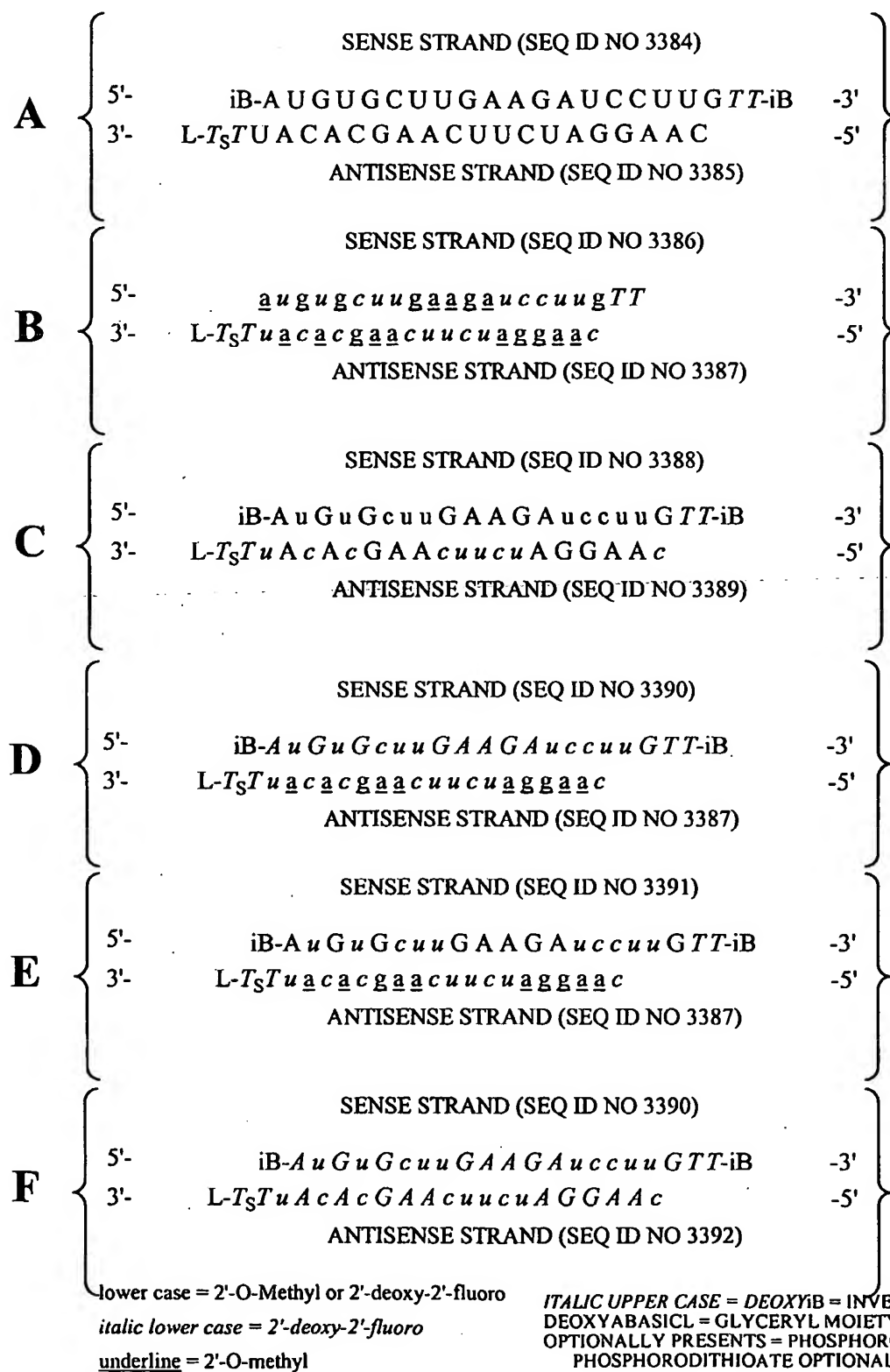
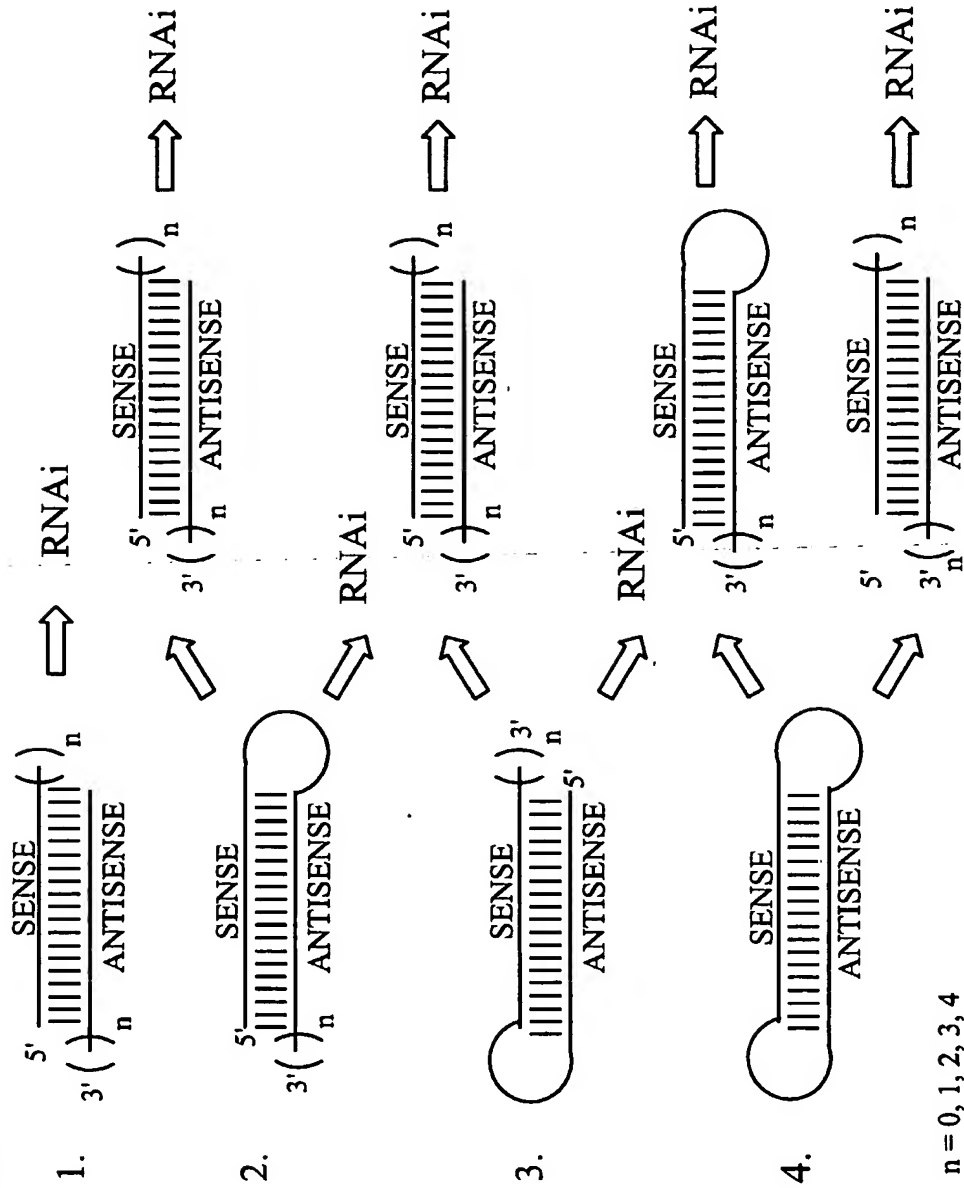
Figure 5

Figure 6



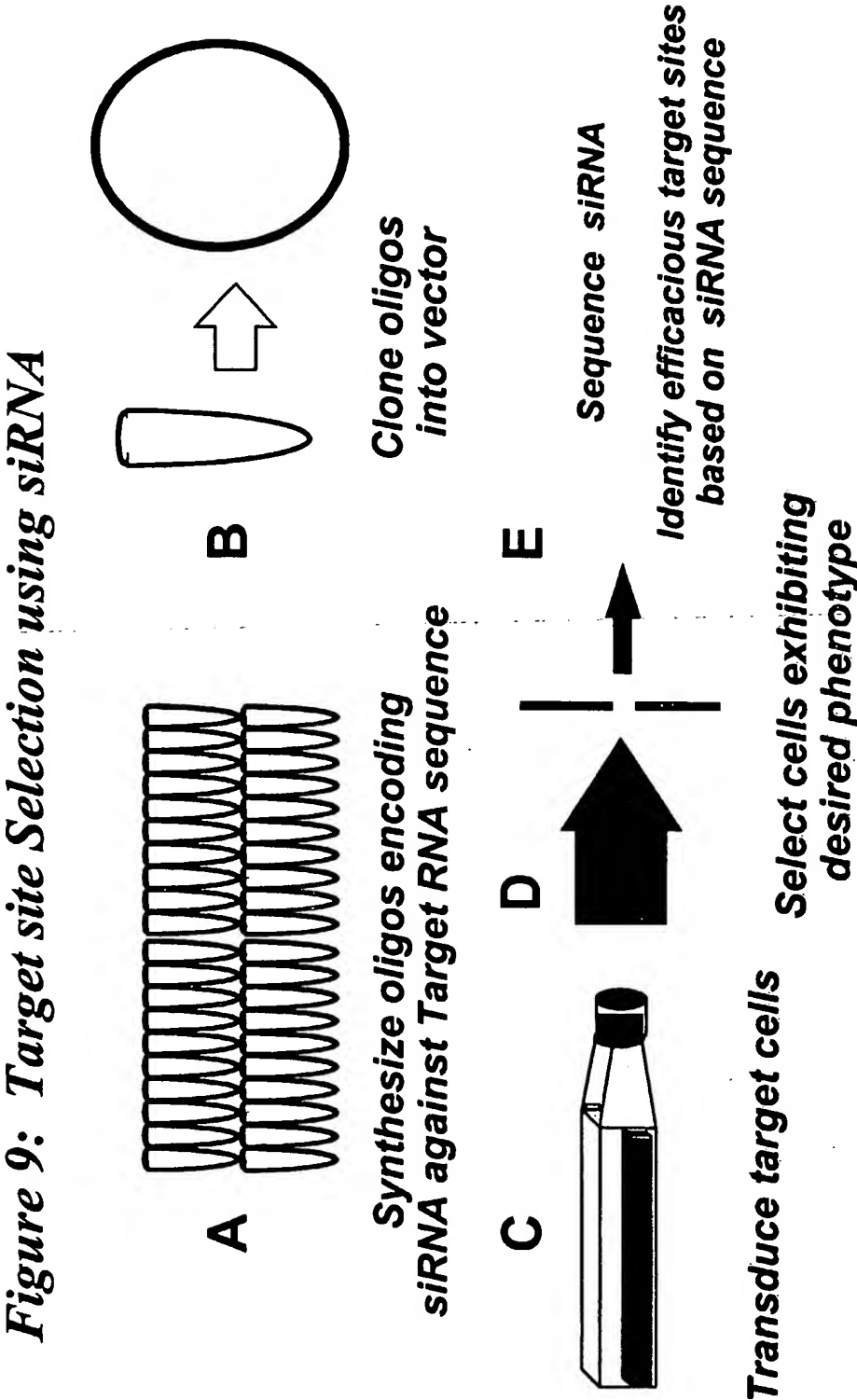
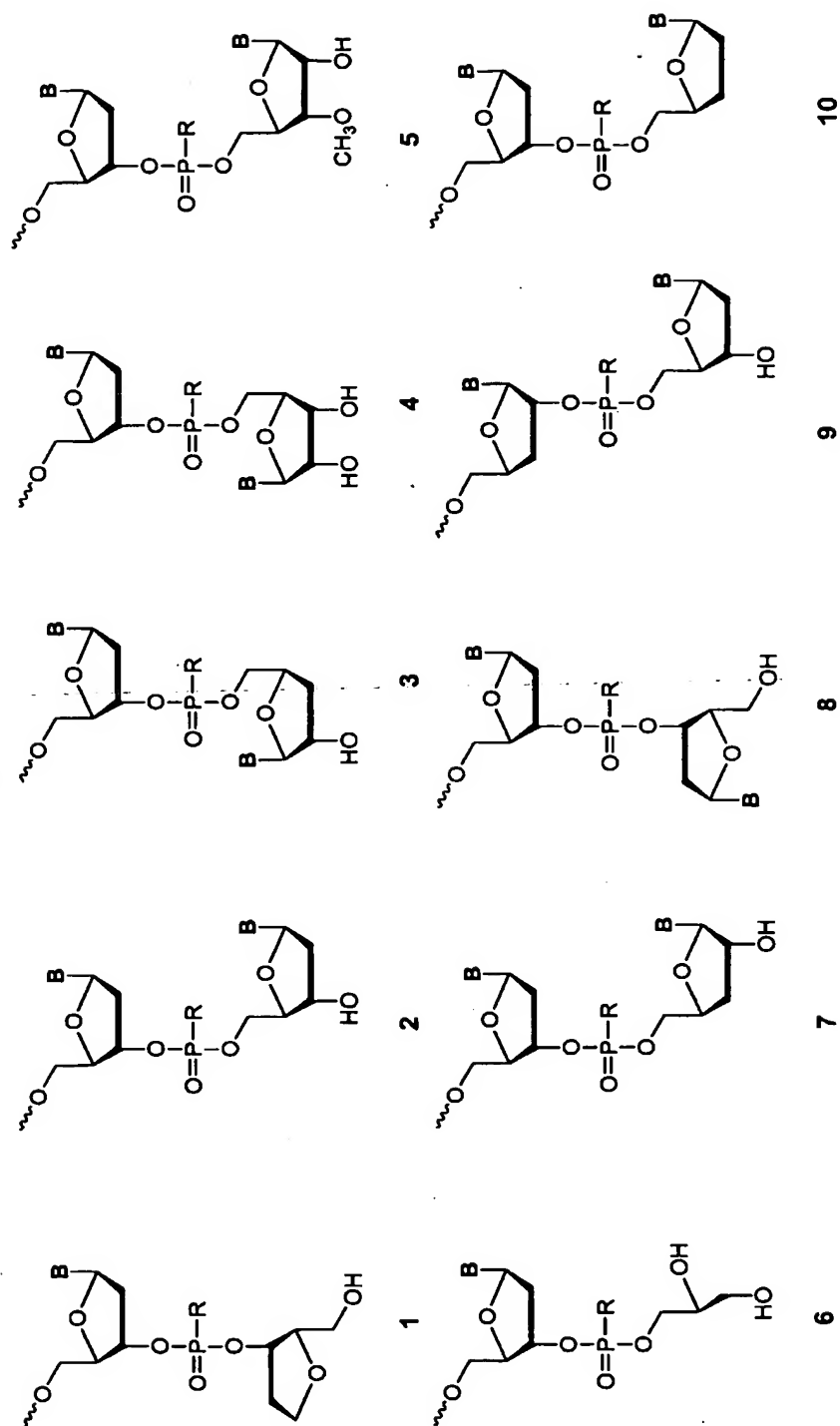


Figure 10

R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
 B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy

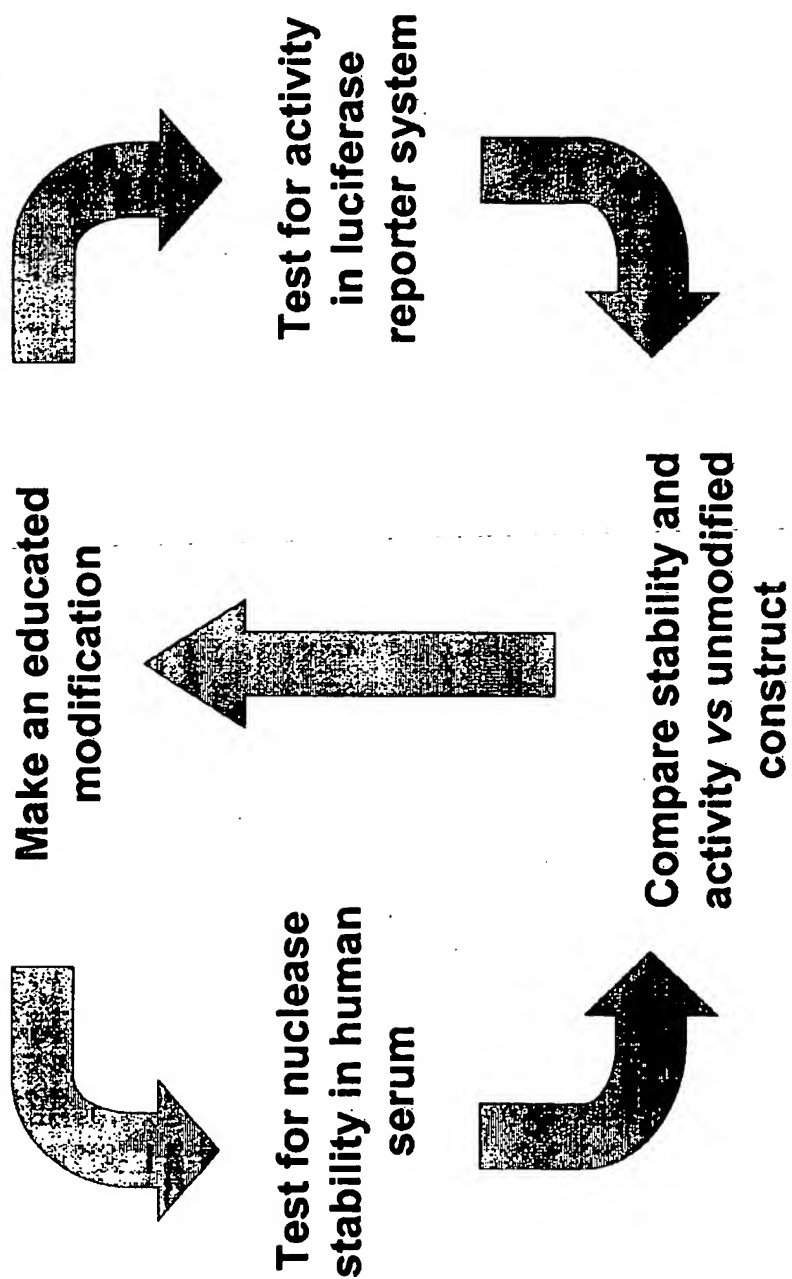


Figure 12: Phosphorylated siNA constructs

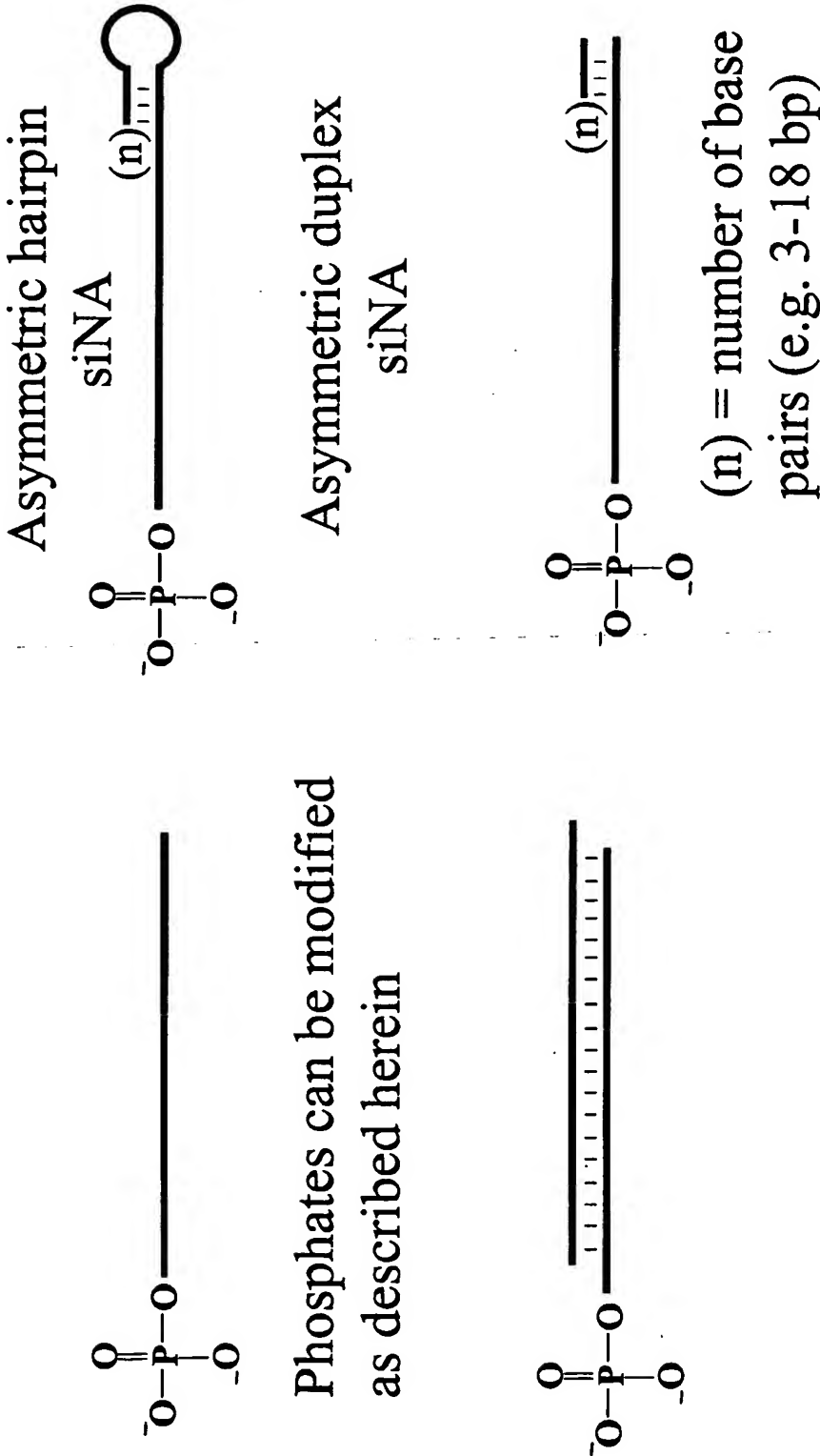


Figure 13: 5'-phosphate modifications

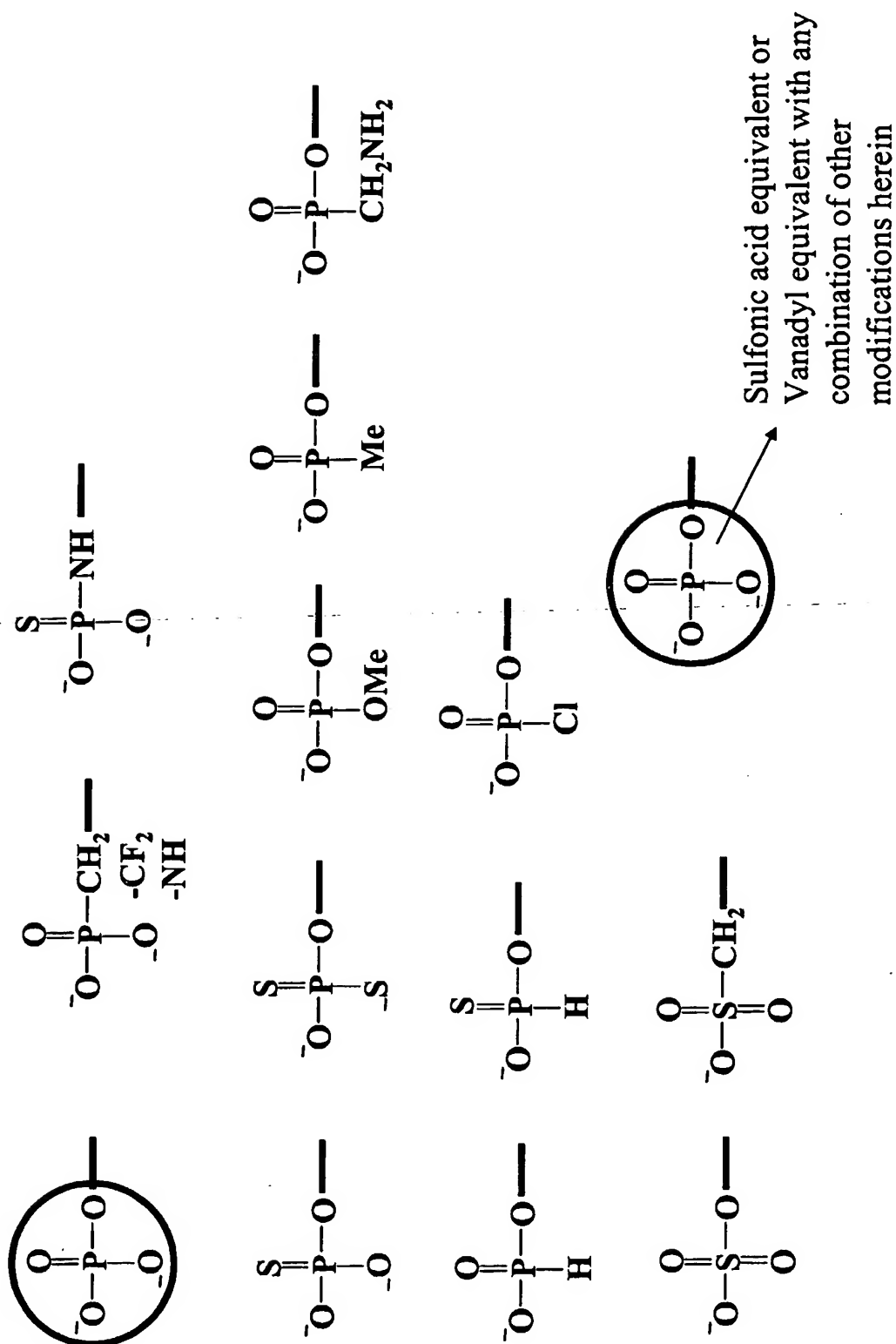


Figure 14A: Duplex forming oligonucleotide constructs that utilize palindrome or repeat sequences

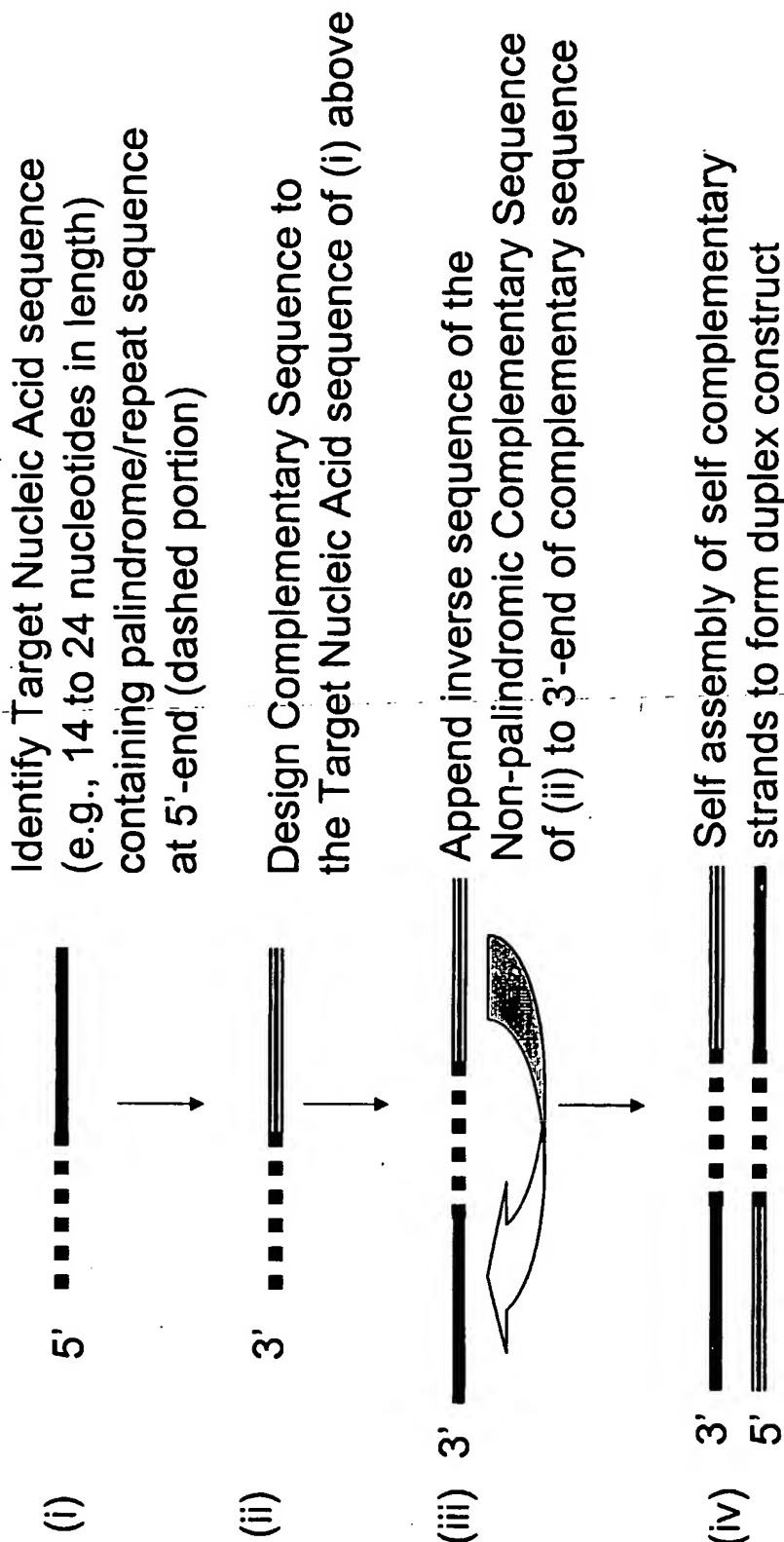


Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence

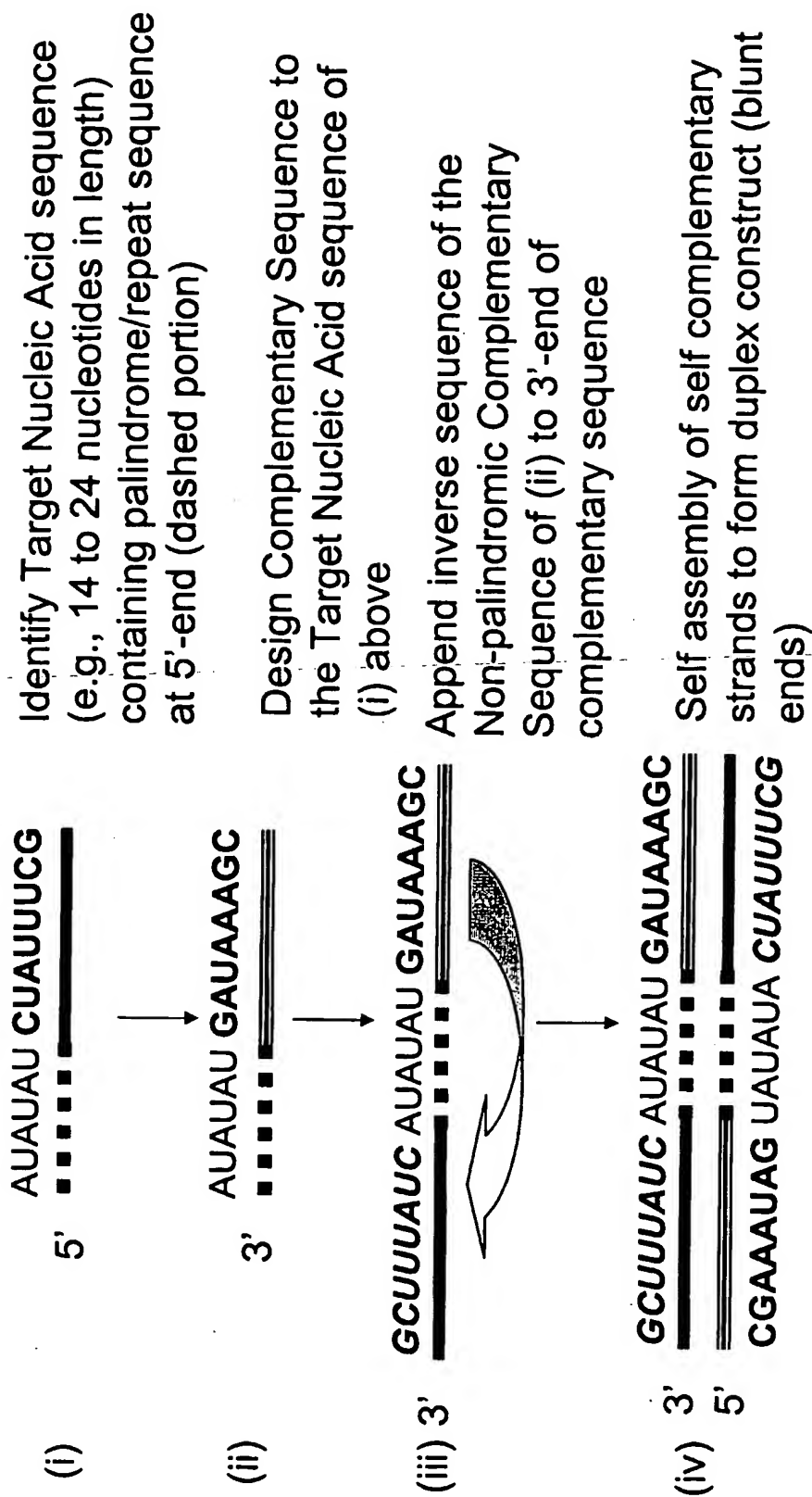


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

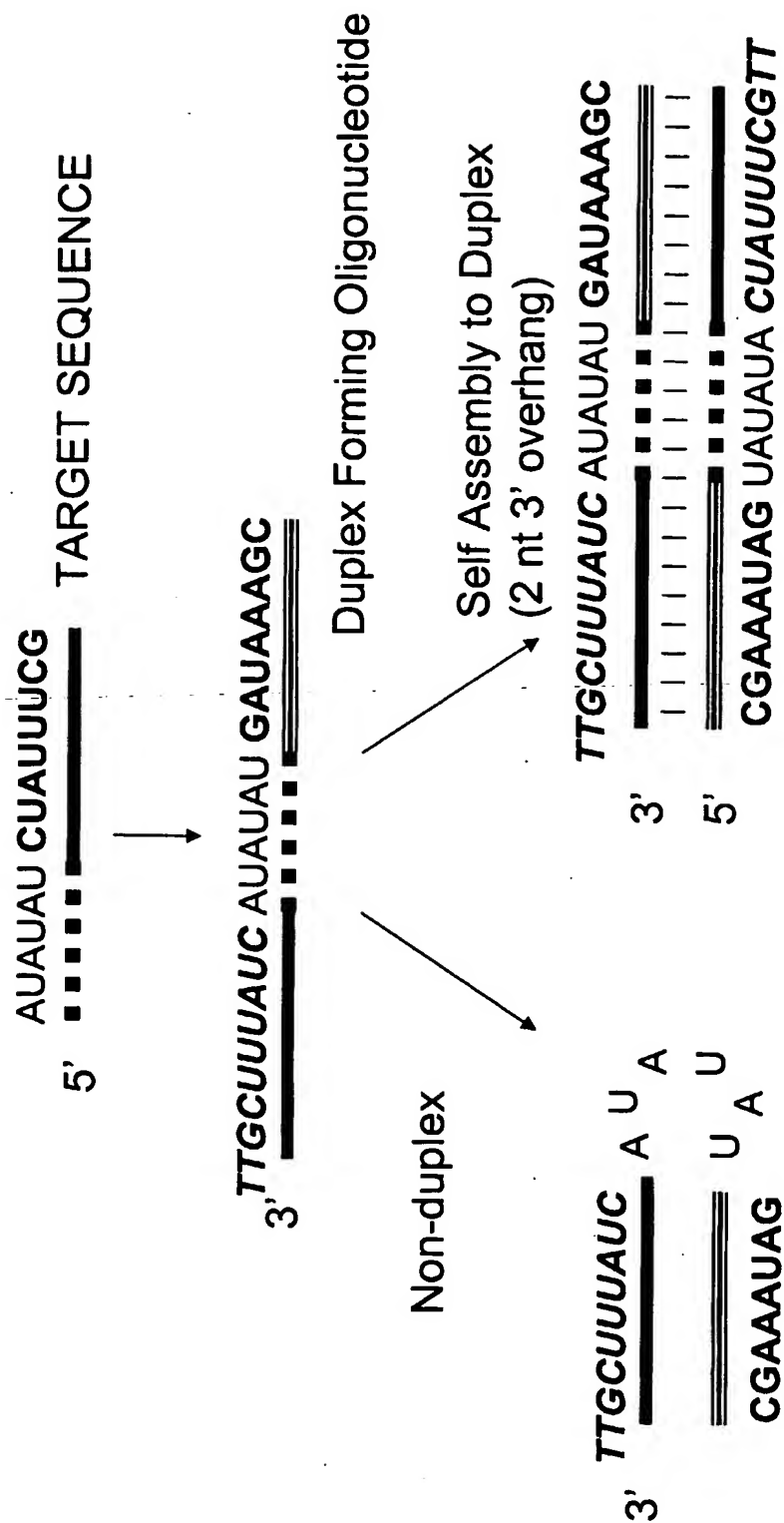


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression

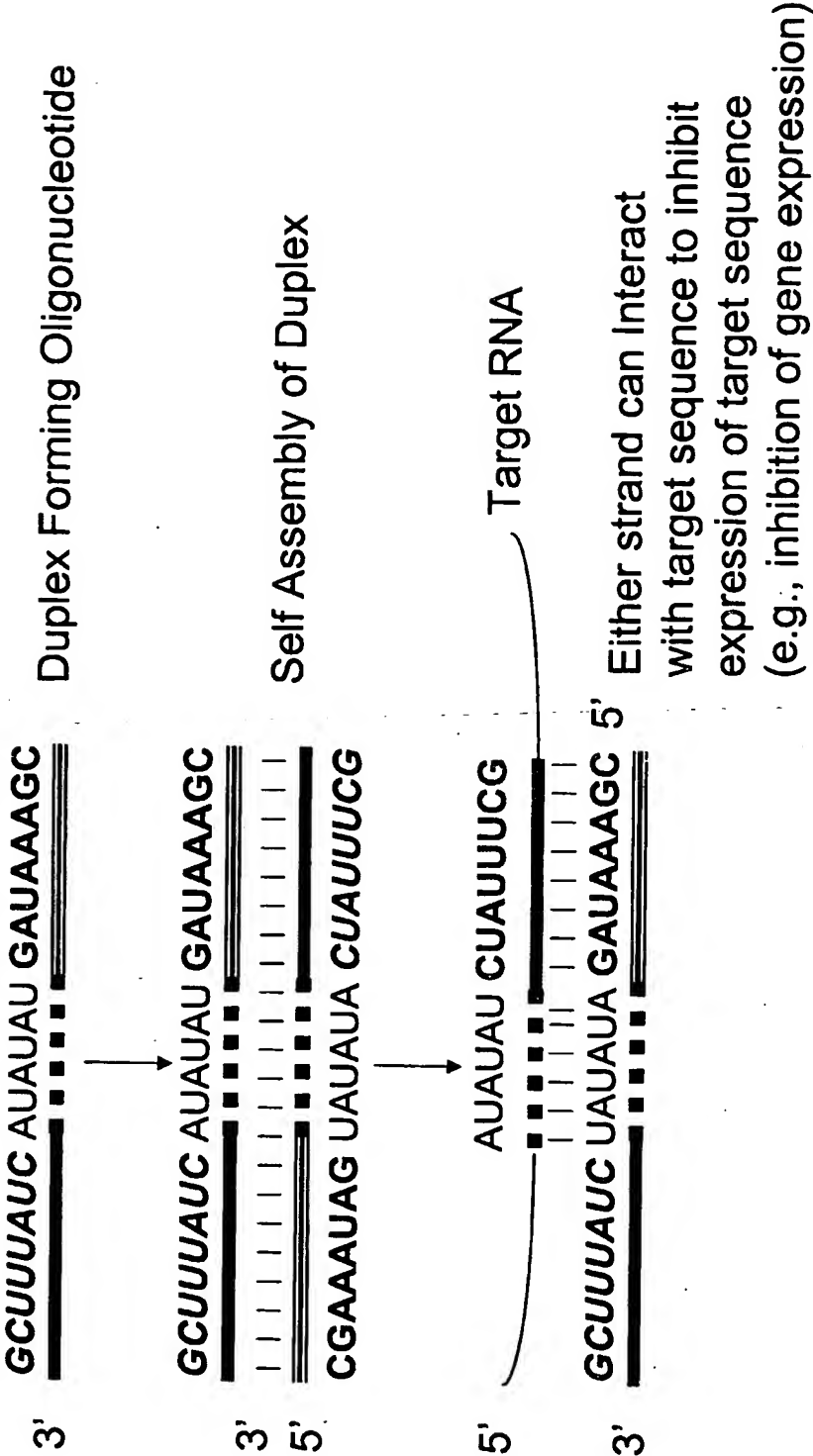


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences

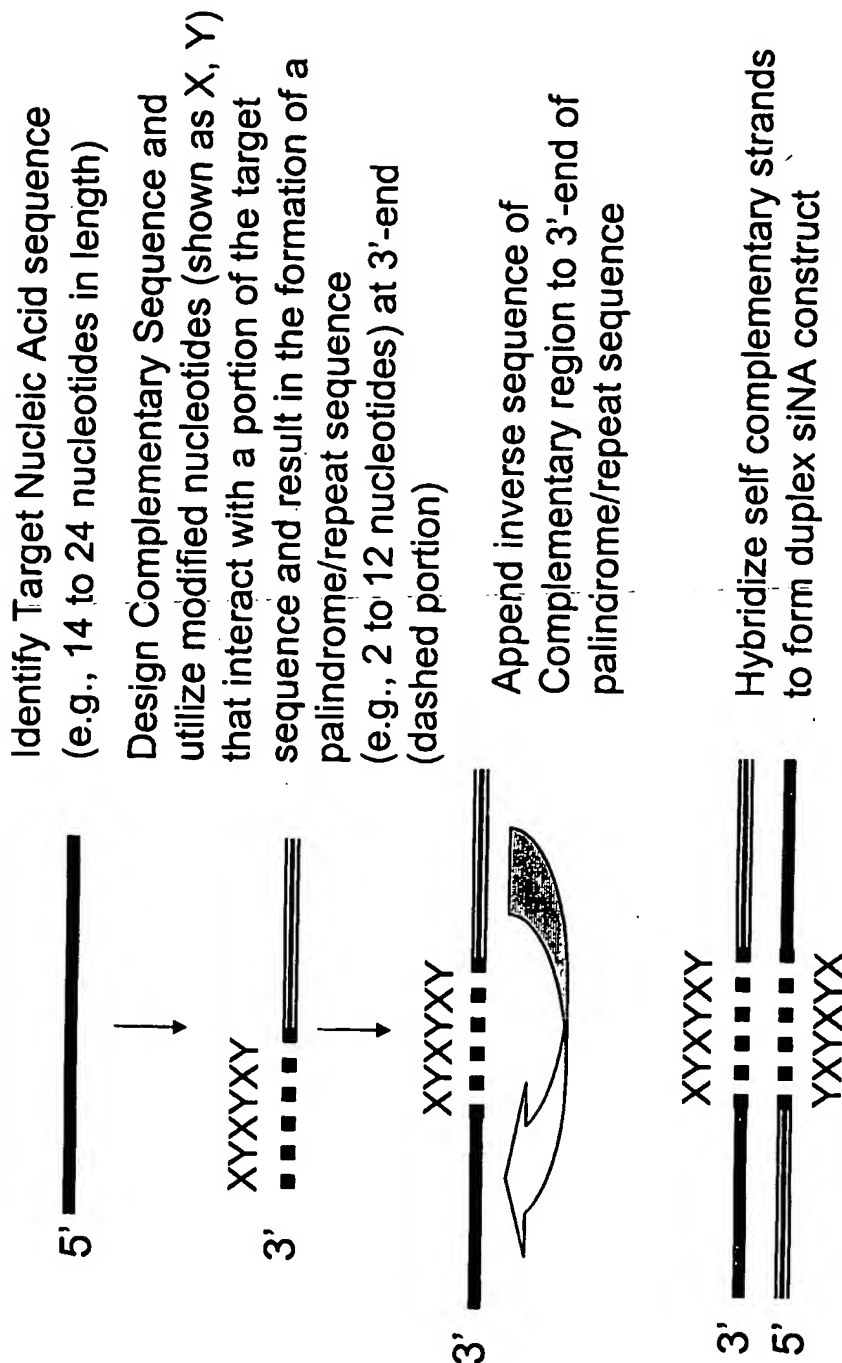


Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

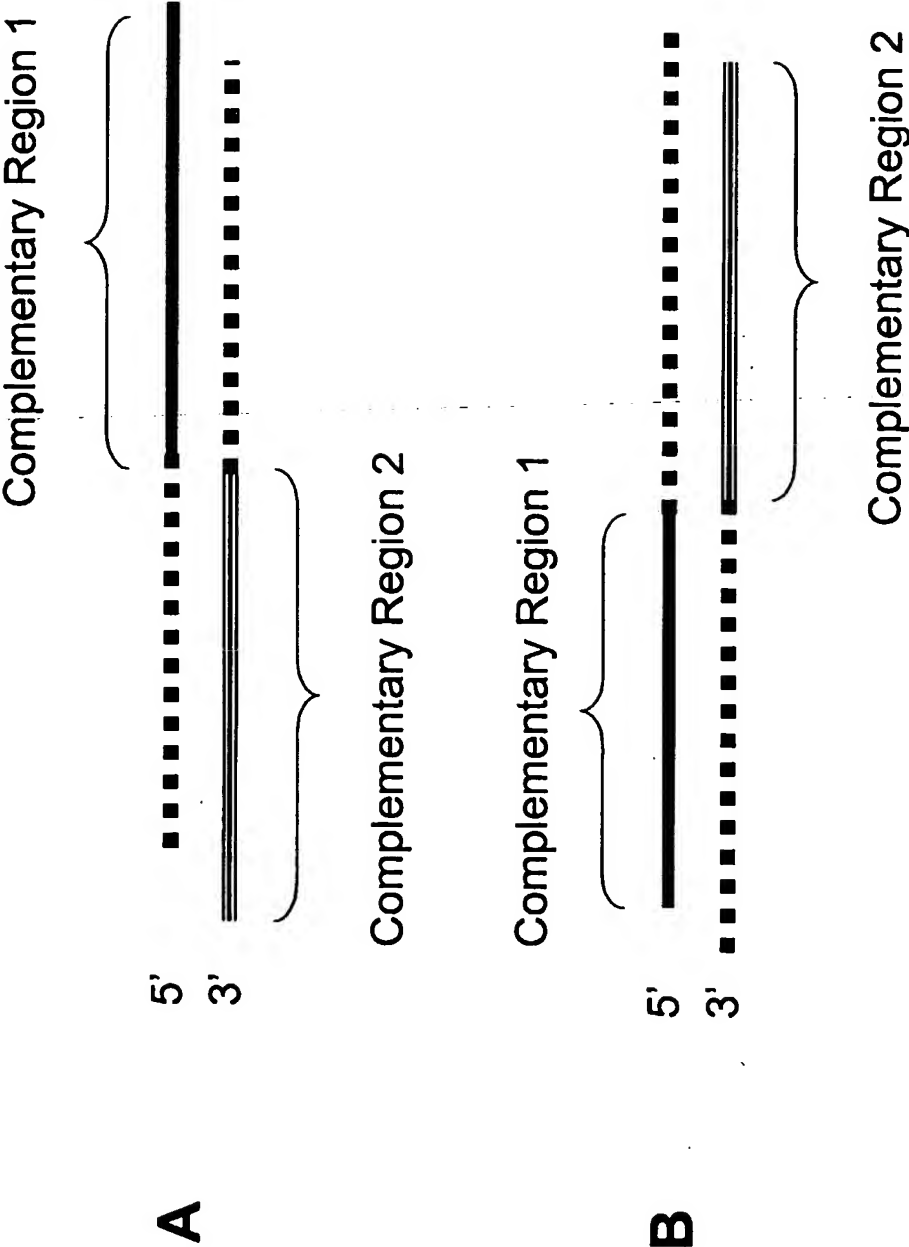


Figure 17: Examples of hairpin multifunctional siNA constructs with distinct complementary regions

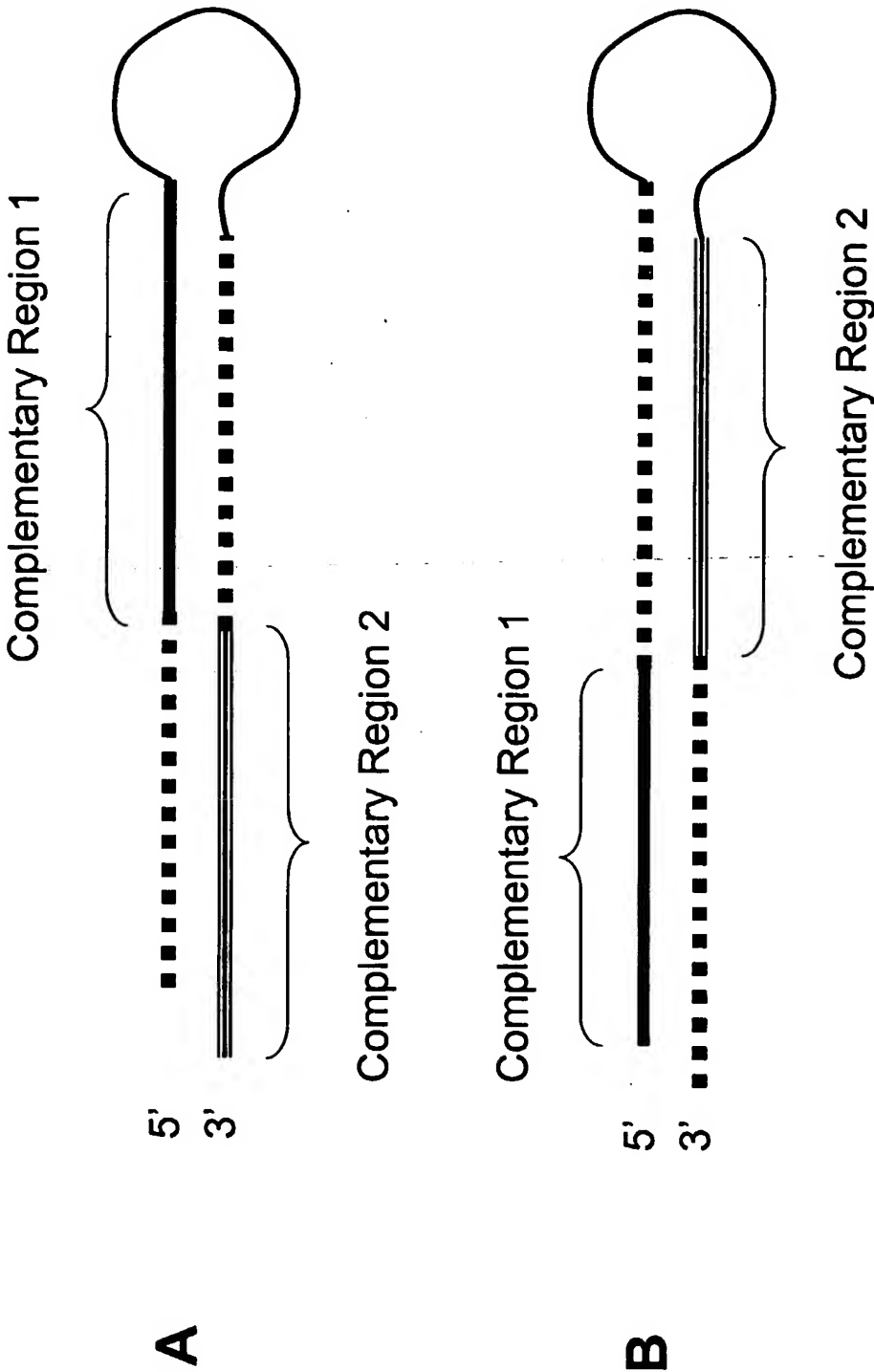


Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

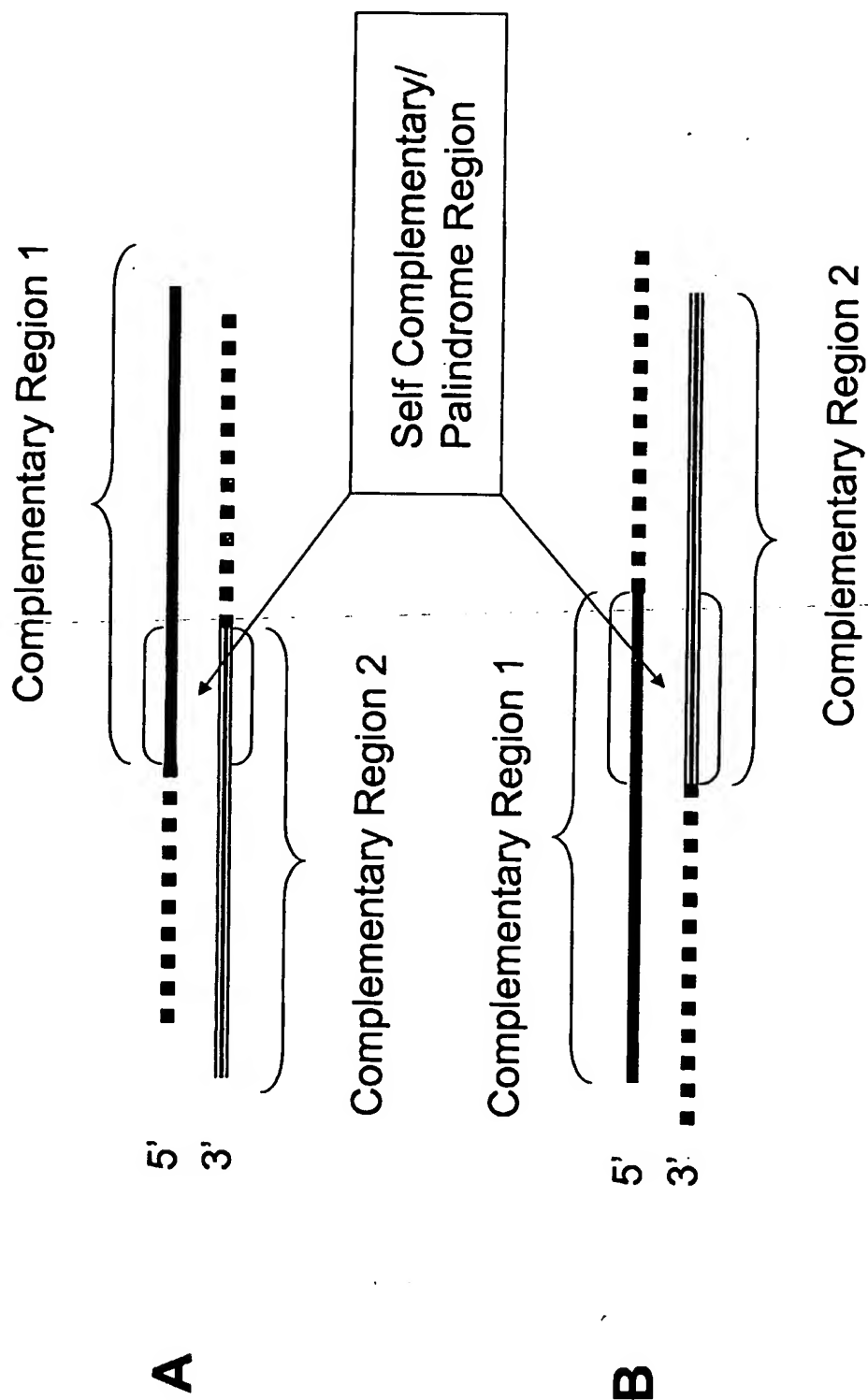
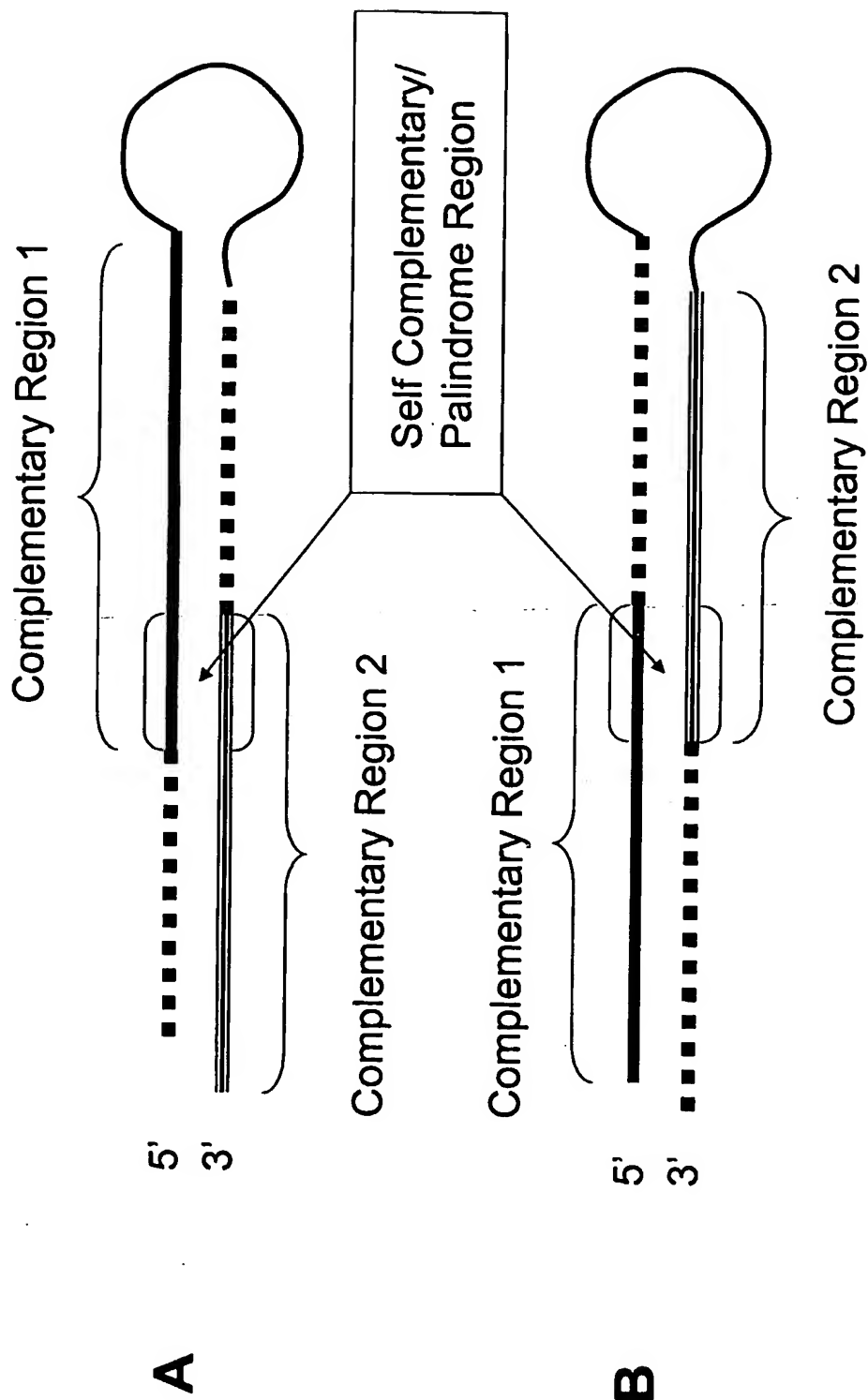


Figure 19: Examples of hairpin multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region



**Figure 20: Example of multifunctional siNA targeting two separate
Target nucleic acid sequences**

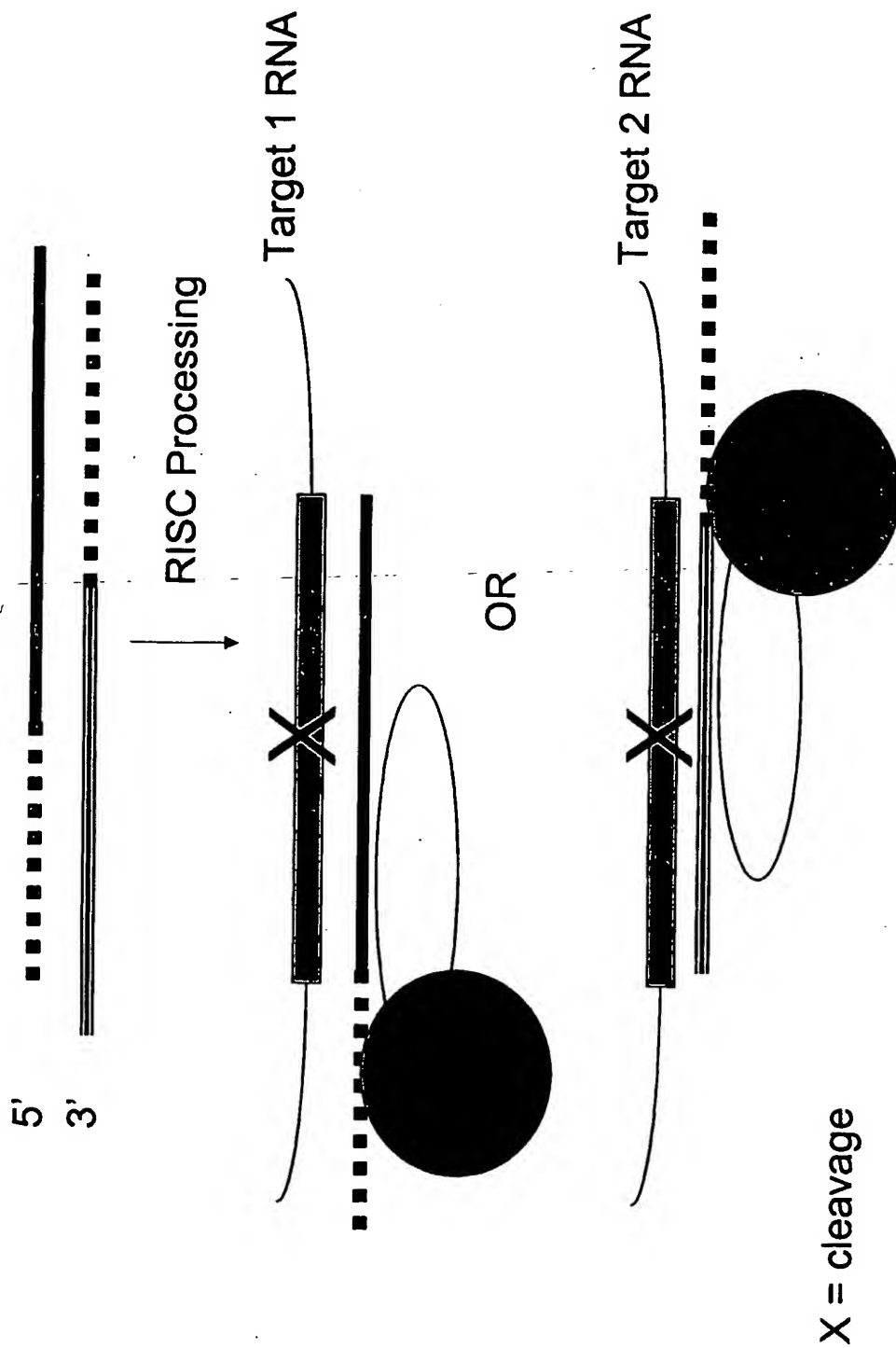


Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence

